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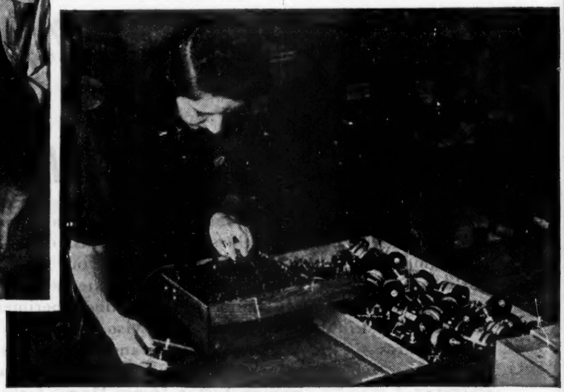

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ADDRESS OF THE PRESIDENT OF THE ROYAL SOCIETY[1]

By Sir HENRY DALE, O.M., G.B.E.

THE annual number of *Obituary Notices of Fellows of the Royal Society,* published to-day, and the names which have just been read to us remind us of the losses the society has suffered.

Allow me first to make brief mention of the last service rendered to the society by one who had long been devoted to its interests, and whose name is among those of the fellows whom death has taken from us during the past year. Sir Henry Lyons, who was our foreign secretary for a year, and then achieved so much for the society in his full term of service as treasurer, had acquired in that period a deep interest in the handling of the society's business and in the changes in its structure and its administration over the centuries of its history. He devoted the last four years of his life, under conditions which must have deterred any less resolute enthusiast, to the writing of a historical account of the administration of the Royal Society under its charters, and at the time of his death, last August, he was eagerly awaiting its publication, which war-time difficulties had long delayed. This long-expected contribution to our history was published a few weeks ago, and the society will welcome and cherish it, not only as a record of value and interest in itself, but in memory of one to whose devoted labors the society and its fellows owe so much.

A year ago I reported to the society that our biological secretary, Professor A. V. Hill, had left us on an important mission to India. The council of the society, at the invitation of the Indian Government, had nominated Professor Hill to visit India to see its problems for himself, so that he might offer his advice on scientific matters in general and, in particular, on the adoption for India of a new and progressive program of research and enterprise in science and its applications. From all sources—from the Viceroy and the Secretary of State with their official colleagues

[1] At the anniversary meeting, November 30, 1944.

and counsellors, and directly from our own colleagues, the Indian men of science—we have had evidence of the unqualified success of this mission of cooperation and good-will. We had nominated Professor Hill with a full confidence in his personal and scientific qualifications for such an undertaking. We knew, however, that the success of his mission would depend even more on the response made to his appeal by India's men of science. To succeed, he must find them sharing his own conviction, that only a large and generous promotion of scientific and technological development in India would open for the teeming millions of its peoples any prospect of the advances in nutrition, health, prosperity and culture required to fit them for their proper place in such a world civilization as we shall soon be striving to rebuild on firmer scientific foundations. The response of India's men of science has been no more in doubt than that of its Government. We sent Professor Hill to hold out the right hand of cooperation; India has sent us six of its scientific leaders to grasp it here in Britain, and we rejoice to have them with us to-day.

In accordance with a plan which I mentioned here a year ago, the first meeting of the society to be held outside this country, in all its long history, duly took place on January 3 of this year, on the occasion of the meeting of the Indian Science Congress in Delhi. The Viceroy, Lord Wavell, honored the meeting with his presence, and Professor Hill, as a vice-president, was able to give formal admission to two of our Indian fellows, Professor Bhabha and Sir Shanti Bhatnagar, and to receive their signatures on a special sheet of parchment. India's prompt and generous response to the invitation which Professor Hill extended has now brought Sir Shanti Bhatnagar here as a member of the return mission, so that he has been able already to sign the Charter Book itself. We shall hope that opportunities will yet occur for all Indian men of science who have been, or will in the future be, elected to our fellowship, to come here to the society's home and to inscribe their names in the book which our fellows have signed since 1662. This, our ancient and now historic Charter Book, is largely representative, in its earlier pages, of the springtime of modern science, not only in this country, but in all the western world; and we desire that it shall now also bear witness to a growing freedom of scientific contact and interchange with the great center of eastern culture, from which our visitors have come. Their journey to Britain, and later to Canada and the United States of America, should mark the beginning of a new era of collaboration in science between India and the rest of the world, growing ever easier and more intimate as the means of world transport, with the added impetus which war's demands have given, attain yet higher levels of speed and safety.

Our Indian colleagues are coming to the end of a visit which, we hope, has given them a new insight into the scientific activities and organization with which this country is still meeting the demands of war, and preparing for the tasks which will later have to be shouldered by a tired though triumphant country, in a largely devastated world. We hope that they will have learned, perhaps from our failures as well as from our achievements, lessons which will have applications of real value to their own country's scientific problems. All fellows of the Royal Society have been glad to know that our apartments have served our Indian guests as an official home and a point of departure for their various visits and engagements, and that Professor Hill has thus been able to keep a close and friendly eye upon this gratifying fulfilment of his hopes and his plans. Two days ago this visit of our Indian colleagues, nearing its end, reached also its climax, when their Majesties, the King and Queen, were graciously pleased to receive them, and thus to show their interest in the promise of a closer understanding and comradeship in science between India, the United Kingdom and the whole of the British Empire.

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I ought to make further brief reference to another matter on which I spoke in some detail last year, namely, the accommodation provided by the nation for those scientific societies which, according to the pattern and tradition of our own, devote their activities to the promotion of natural knowledge for the general advantage, without reference to private interests or to professional status and discipline. Such provision had been accepted as a national obligation as early as 1778. The quarters at present provided, here in Burlington House, represent the allotment made in 1869 to the societies which then achieved such recognition. Since that date no enlargement or material alteration has been made, and there seemed to be no prospect of any, either for the societies admitted 75 years ago, or for others whose claims to such privilege have later appeared. Even the accommodation thus assigned in 1869 appears to have been only a remainder, after the major part of an earlier and more generous plan for science had been diverted to other purposes by intervening claims. In 1869, we should remember, the study and promotion of the sciences had hardly been recognized as a life's occupation, except for a few determined devotees; science was at that date still largely a matter for the leisure of cultured amateurs. It is no matter for surprise, therefore, that accommodation then regarded as acceptable should now be found to make grossly inadequate provision for some of the more important of present scientific needs, and none at all for others.

After I had drawn public attention to this anomaly last year, we were asked by several of the specialist societies concerned, to take appropriate action with the Government. We approached the Lord President of the Council, Mr. Attlee, and on October 13, with the Chancellor of the Exchequer, Sir John Anderson, and the Minister of Works and Buildings, Lord Portal, he kindly received a deputation representing all the societies which have been housed here sinc 1869, and several others for which the Government has hitherto made no provision. Apart from the special and urgent needs of some of the societies, the case was fully presented for the inclusion, in any scheme for the rebuilding of London, of a center adequate to accommodate the principal scientific societies on a well-coordinated plan, and so placed and designed as worthily to symbolize the central importance of British science, for the cultural as well as the material aspects of the civilization of this nation, and, indeed, of the world. The ministers gave a careful and sympathetic hearing to the statement of our claims, and asked us to furnish quantitative data, as a basis for their further consideration of the problem.

With the outcome of the war even more certain, there can be no relaxation yet of the demand on what our scientific effort can contribute to the hastening of its end. It is none the less our duty to begin to look further ahead and to prepare for the part which science must play in the world which will follow. The needs of alliance in war have evoked, especially between the two great branches of the English-speaking nations, a closer interchange and collaboration in science, between men of different national traditions and loyalties, than has ever before been a matter of organized policy. It is not too early to begin to consider to what degree, and in what form, such a collaborative effort should be continued into the conditions of peace, and extended to scientists of international good-will throughout the world. Even in the twenty years of uneasy armistice which ended in 1939, a measure of cooperation among the world's scientists was achieved, which held promise as a potential agent of international understanding. Our traditions go back to days when our fellows belonged to a community embracing all Europe in its enthusiasm for the new experimental philosophy, and the Royal Society

SCIENTIFIC APPARATUS AND LABORATORY METHODS

LYOPHILIZATION APPARATUS

The accompanying diagram (Fig. 1) illustrates a simple, rugged, inexpensive lyophilization apparatus which has been used successfully for moderately large-scale laboratory work.

Approximately 50 pounds of dry ice, broken into small lumps by means of an ice chopper, are required to fill the insulated chamber. Effective cooling is thus maintained without organic solvents and without further attention for at least 24 hours of operation. For shorter periods of lyophilization, the dry-ice requirement can be reduced by a false bottom in the dry-ice chamber.

The cylindrical welded steel receiver is unbreakable and has a condensing capacity of approximately 6 liters. The manifold is constructed of pyrex glass and is connected to the receiver by means of a rubber stopper. Obviously, the design of the manifold and the number of outlets can be varied to suit individual requirements. A useful design consists of four outlets spaced at 90° intervals to which round bottom pyrex-glass flasks of 1- or 2-liters capacity can be attached either by ground-glass joints or rubber stoppers. The flasks are filled to about one third of their

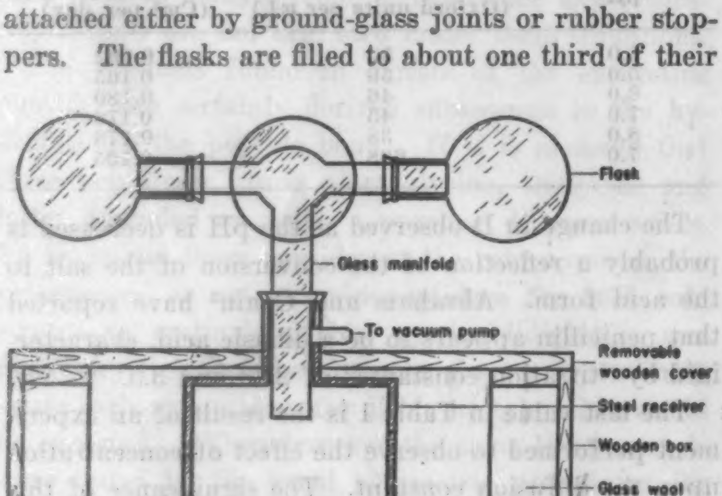

Fig. 1

capacity, and before they are attached to the manifold, are rotated in a dry-ice-solvent mixture to freeze the material in a thin layer.

A pressure of approximately 0.2 mm can be attained rapidly and maintained by means of a mechanical high-vacuum pump of suitable capacity. Approximately 1,200 ml of water (300 ml in each of 4 one-liter flasks) can be removed in 20 to 24 hours.

As suggested by Campbell and Pressman[1] a piece of cotton gauze cemented over the manifold opening effectively prevents loss of small amounts of dry material during lyophilization. Small leaks which may develop in the rubber or ground-glass joints when the system is subjected to high vacuum can be prevented by the liberal application of a sealing compound such as Apiezon Sealing Compound Q.[2] A sealing compound of this type, which is plastic at room temperature, can be applied quickly and easily and can be stripped off and reused. Furthermore, sealing connections from the outside in this manner obviates the use of greases, which may contaminate the material during lyophilization or during removal of the dry material from the flasks.

The usefulness of the apparatus can be increased by providing the cabinet with casters so that it may be moved as required. The vacuum pump, pressure gauge and a cold trap for protecting the pump can also be mounted on a caster-equipped table so that it can be used either with the lyophilization apparatus or with other equipment.

Adrian F. Pomes[3]
George W. Irving, Jr.

Southern Regional Research Laboratory,[4]
New Orleans, La.

[1] D. H. Campbell and D. Pressman, Science, 99: 285, 1944.
[2] May be obtained from the James G. Biddle Company, Philadelphia.
[3] On military leave.
[4] This is one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

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Cole, F. J. *A History of Comparative Anatomy.* Illustrated. Pp. viii + 524. Macmillan Company. $7.00. 1944.

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After I had drawn public attention to this anomaly last year, we were asked by several of the specialist societies concerned, to take appropriate action with the Government. We approached the Lord President of the Council, Mr. Attlee, and on October 13, with the Chancellor of the Exchequer, Sir John Anderson, and the Minister of Works and Buildings, Lord Portal, he kindly received a deputation representing all the societies which have been housed here sinc 1869, and several others for which the Government has hitherto made no provision. Apart from the special and urgent needs of some of the societies, the case was fully presented for the inclusion, in any scheme for the rebuilding of London, of a center adequate to accommodate the principal scientific societies on a well-coordinated plan, and so placed and designed as worthily to symbolize the central importance of British science, for the cultural as well as the material aspects of the civilization of this nation, and, indeed, of the world. The ministers gave a careful and sympathetic hearing to the statement of our claims, and asked us to furnish quantitative data, as a basis for their further consideration of the problem.

With the outcome of the war even more certain, there can be no relaxation yet of the demand on what our scientific effort can contribute to the hastening of its end. It is none the less our duty to begin to look further ahead and to prepare for the part which science must play in the world which will follow. The needs of alliance in war have evoked, especially between the two great branches of the English-speaking nations, a closer interchange and collaboration in science, between men of different national traditions and loyalties, than has ever before been a matter of organized policy. It is not too early to begin to consider to what degree, and in what form, such a collaborative effort should be continued into the conditions of peace, and extended to scientists of international good-will throughout the world. Even in the twenty years of uneasy armistice which ended in 1939, a measure of cooperation among the world's scientists was achieved, which held promise as a potential agent of international understanding. Our traditions go back to days when our fellows belonged to a community embracing all Europe in its enthusiasm for the new experimental philosophy, and the Royal Society

will have a particular duty to be among the leaders in the resumption of international activities in science, and to use all its influence to establish these on an ever wider and firmer basis. We have a standing committee on international relations in science, with our foreign secretary appropriately as its chairman, to prepare for what action the society can usefully undertake or promote, as the opportunity presents itself. Meanwhile we may observe other signs that the spirit of international friendship and recognition in science is beginning to move again, even while the chaos of war is still with us. Among such signs, we may note that one of the committees which, since their foundation in Stockholm, have awarded the Nobel Prizes with unchallenged impartiality among the scientific discoverers of all nations, has resumed its awards this year. We in this society have welcomed the return to London of a group of distinguished French leaders in science from the United States of America, whither they had escaped from the hostile occupation of their country. We have been able to share their rejoicing at the liberation of France, and to welcome here others who had remained there, often in hiding and always in peril, as leaders in the steadfast resistance opposed by all but a negligible minority of the French men of science to the enemy's demands for their collaboration. The society had the pleasure of providing a special opportunity for our fellows to meet our French colleagues, with those from other allied countries who have long been in exile here during enemy occupation of their homelands. We are glad to think that new and lasting bonds of comradeship in science have been created for us with those who have been our country's wartime guests, and through them with all the men of science in the countries which they represent.

The society had recently the opportunity of showing its interest in the revival of international scientific cooperation in another special connection. From October 16 to 19 a small international conference met here, under the auspices of the Health Organization of the League of Nations, to discuss the creation of an international standard of reference for penicillin and the definition, in terms of this, of a unit of activity. Though the league has failed tragically of its central purpose, it has less conspicuous achievements to its credit, and science has an interest in ensuring the permanence of some of these. I have myself had the privilege of taking part in the activities of an international commission under the Health Organization of the league, which succeeded, in the years between the wars, in obtaining world-wide acceptance of standards and units of activity for a whole range of modern remedies—antitoxins, hormones, vitamins and certain drugs—the strength of which could only be determined by direct biological measurements of the specific activity, in comparison with that of a fixed standard preparation in each case. Insulin was an early instance of a new remedy requiring such intervention; its general use for the treatment of diabetes could not have attained the present level of safety and effectiveness, unless a world-wide uniformity on these lines had replaced the chaos of widely different units in different countries, which was threatened in 1923. And now research has produced another new remedy, penicillin, the success of which, in the treatment of a range of dangerous infections, has also had such a dramatic quality that its reputation has spread rapidly beyond our scientific community and caught the interest even of a war-distracted world. Here, indeed, was a discovery which could rank as a major contribution of science and to the mitigation of the suffering which war inflicts, and, at the same time and no less, as a gift of healing to mankind at peace. The needs of war had given a stimulus to the researches which proved penicillin's remedial value, but its rapid production on an adequate scale had to face greater difficulties in our own country, where material and human resources had been more completely absorbed by earlier requisitions, than in the United States. So the present position was reached, in which, as we are proud to recognize, the existence of penicillin and then, after a decade, the methods by which it could be separated in sufficient purity to demonstrate its brilliant possibilities as a remedy, were discoveries made here in England, while, in the further researches and technical developments needed for its large-scale production, our American colleagues have played a major part.

Thus early in its history, therefore, penicillin and its applications had become a matter of international concern; and, though war had restricted the work in this field almost entirely to scientists of the English-speaking peoples, and had brought them into an unusual intimacy of cooperation, progress had been so rapid and action so urgent that there was a real danger of a divergence of meaning in the terms used to express its activity and define its dosage, even among the few countries already using it. Prompt action was required to avert this by accepting a common standard of reference; and, when the proposal of a conference for this purpose was made from this country to the League of Nations Health Section, we were grateful to our colleagues from the United States, as well as from Canada and Australia, for the generous promptitude with which they agreed to make the journey to England, so as to meet with us here in London. After all arrangements for the holding of the conference here had been completed, the liberation of Paris opened a new possibility; Dr.

Tréfouel, now director of the Pasteur Institute in Paris, was able at the last moment to accept an invitation to join us, and thus to give our deliberations, and our eventual agreement, a wider international basis. To illustrate how rapidly a divergence may arise under present conditions, I may just mention the fact that several different penicillins have now been recognized, produced by variations in the metabolism of the growth, possibly due to mutations of the mold itself, possibly to changes in the nutritive conditions offered to it by the medium or the cultural method employed. Three such varieties of penicillin have already been isolated in pure condition, and distinguished by certain chemical characters; but, while English workers had come to refer to these as Penicillin 1, 2 and 3, their colleagues in America spoke of Penicillin F, G and X; and it was not until they met round the table in our council room a few weeks ago, but then in less than 10 minutes, that they became quite certain of the identity of 1 with F, of 2 with G and of 3 with X. All these penicillins have the specific remedial action in high, though not quite identical degrees, and there are probably differences, still to be explored, in their proportional efficiencies against different infective organisms. When once their identities were thus put beyond doubt, however, the small conference had no hesitation in deciding, for the present, to use as the common basis of reference a sample of the penicillin which is predominant in most preparations now available, and most easily obtained as a pure salt in adequate quantities. The unit could then be defined as the activity of a precise, though very small weight—0.6 μg—of a particular sample of the perfectly dried, crystalline sodium salt of Penicillin 2 or G; and the unit thus chosen for definite fixation, and for international recognition henceforward, was, by a unanimous choice, so defined as to be as closely equivalent as possible to the unit first propounded by Sir Howard Florey's team of collaborators, and widely known as the "Oxford" unit.

The International Standard for Penicillin is thus added to an already numerous series, of which the custody, on behalf of the League of Nations Health Organization, has been shared by our own National Institute for Medical Research with the State Serum Institute of Denmark, at Copenhagen; and all these standards, we may hope, will be available for transfer to whatever international authority may be established in succession to the league, as a tangible and material result of genuinely international collaboration, which the league has been able to initiate and maintain among men of science, to the permanent advantage of the world.

Though penicillin has rightly made a special appeal to the imagination and sympathetic interest of a wide public, it is, of course, only one out of a varied range of inventions and discoveries, hastened by the stimulus of war's demands and produced, in many cases, behind the veil of its secrecy, but ready, when peace returns, to take their proper place as new gifts to the welfare and the civilized progress of mankind. From what has already been made generally known, it is clear that we may look forward to revolutionary advances in the means of communication and in the speed and safety of travel across the world, and in methods of controlling insect pests and the diseases which insects convey; and these are but a few examples of the gains which we and the world may hope to set against the tragic loss and sacrifice of the years of war. There were probably few who even suspected in 1939 that science, in countries then so dangerously unready, would find itself, before the war ended, in its present position of central importance. None of us, I think, would claim more for science, even now, than to have played in this war a part of growing predominance in the provision for the fighting men of the material means of warfare, without which their heroism and sacrifice could not have prevailed. Even that duty, loyally accepted, is one from which the scientific community of the free nations must long for the release which victory will bring. But, while the operations of war have come to depend on science to a degree beyond all earlier experience, it can not be doubted that little more than a beginning has yet been made in exploiting the possibilities of destruction, which science could progressively offer, if the world should continue thus to misuse it, and if science were still on offer for such ends. Allow me to quote a passage from a letter which the Prime Minister, whom we are proud to number among our fellows, wrote a year ago to Professor Hill, in sending his greetings to Indian men of science.

"It is the great tragedy of our time," wrote Mr. Churchill, "that the fruits of science should by a monstrous perversion have been turned on so vast a scale to evil ends. But that is no fault of science. Science has given to this generation the means of unlimited disaster or of unlimited progress. When this war is won we shall have averted disaster. There will remain the greater task of directing knowledge lastingly towards the purposes of peace and human good." Noble words indeed, and a profession of faith which will find an immediate echo in the hope and the desire of every true man of science. "When this war is over we shall have averted disaster"—surely that is a confidence which every one of us will long to share. It must be clear, however, that Mr. Churchill's reference was to the present threat of disaster, from which the prospect of our escape is even more fully

assured to-day than when he wrote, a year ago. We may be certain that nobody sees more clearly than he that the threat of final disaster to all man's hopes and achievements will not be forever averted, if the possibility of the "monstrous perversion" of science is allowed to remain and to continue its evil growth. Even in the past year our enemies have thrown a new and vivid light on future possibilities, by the new weapons which science has enabled them to put on trial for our destruction. Though a people's unflinching courage and an answering effort of science and organization, together with the progress of the Allied armies over the launching areas, have given us confidence that flying bombs and the like will not affect the issue of this war, the warning which they give, as to what the future might hold, is not the less clear. The writing on the wall must be plain for all to read. If, when the memories of the present war begin to fade, the world should allow science again to be exploited by a nation grasping at predominance by conquest, science will no longer be invoked only as an aid to what valor can achieve by land, sea or air, but as an agent, in itself, of blind annihilation at an ever lengthening range. When we men of science regain that freedom, for the ultimate preservation of which we have loyally accepted, through these tragic years, the bonds of secrecy and submission to authority, we can not put aside with these our proper share in the new responsibility for the future of mankind, which this war's experiences have laid upon the men of good-will in all nations. It is true, indeed, that neither the present abuse of science, nor any possibility of final disaster to civilization, which might come of a future perversion of its powers, can be charged as a fault to science itself; no more, indeed, than we could properly charge to religion, as such, the wars which once devastated much of Europe in its name. But we men of science can not escape from our growing share in the responsibility, in "the greater task," as Mr. Churchill has written, "of directing knowledge lastingly towards the purposes of peace and human good." No man of science has the right to prescribe for another his interpretation in detail of that duty; but there is one aim which may unite us, perhaps for the most effective action within our common grasp, and one which is worthy of all our common influence and effort. Let me quote again from Mr. Churchill's letter: "in this task," he writes, "the scientists of the world, united by the bond of a single purpose which overrides all bounds of race and language, can play a leading and inspiring part." To build anew, and on a firm and broadening foundation, a world community in science, is surely an aim worthy of our utmost effort and devotion; but there can be no swerving from the present duty, and the call on science by war may yet be sterner, before we have won the freedom thus to work for the future of the world.

THE SITE OF ANTIBODY FORMATION*

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EVOLUTION in science is brought about by the discovery of facts and the elaboration of patterns into which these facts will fit. The earliest facts about the formation of antibodies discovered by Metschnikoff and others fitted well into the pattern of the reticulo-endothelial theory of antibody production. However, in recent years additional facts have been brought to light which are difficult to reconcile with this theory,[1, 2, 3, 4] and we have recently presented new facts which seem to be inconsistent with the old concept.[5, 6] The latter lend themselves to the elaboration of a theory which is consistent not only with the old facts but also with the new ones. This new pattern of antibody formation is the subject of the present presentation.

THE RETICULO-ENDOTHELIAL THEORY OF ANTIBODY FORMATION

The reticulo-endothelial theory of antibody formation was widely accepted, undoubtedly because it seemed plausible that the cells which phagocytose and destroy bacteria should also be concerned with the synthesis of antibodies.[7] "It is chiefly this phagocytosis of formed antigens (erythrocytes, bacteria) which has directed the attention to the reticulo-endothelium as the possible source of the antibodies."[8]

There are two important arguments which have been

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[1] L. Hektoen, *Jour. Infect Dis.*, 17: 415, 1915.

[2] J. B. Murphy and E. Sturm, *Jour. Exp. Med.*, 41: 245, 1925.

[3] W. E. Ehrich and W. Voigt, *Beitr. Path. Anat.*, 93: 348, 1934.

[4] A. R. Rich, M. R. Lewis and M. M. Wintrobe, *Bull. Johns Hopkins Hosp.*, 65: 311, 1939.

[5] W. E. Ehrich and T. N. Harris, *Jour. Exp. Med.*, 76: 335, 1942.

[6] T. N. Harris, E. Grimm, E. Mertens and W. E. Ehrich, *Jour. Exp. Med.*, in press.

[7] Annotations, *Lancet*, 1: 654, 1943.

[8] R. H. Jaffe, "The Reticulo-Endothelial System." Handbook of Hematology, Vol. II. New York: Hoeber. 1938.

advanced in support of this theory and which enjoy general consideration. One of these is based on the observation that the output of antibodies may be depressed through blockage of the reticulo-endothelium with phagocytotic material such as iron-sugar, india ink, trypan blue or collargol. In interpreting this finding, it has been argued that the "blockade" acts by interfering with the phagocytic and digestive function of the macrophage, that this cell while engaged in digesting one colloid, could not well take care of another, and therefore could not produce antibodies.

The phagocytic and digestive function of the macrophage can not be questioned. But have we any proof for the contention that this function results in antibody formation? Suppose that Bunting[9, 10] was right when he postulated that the micro- and macrophages merely destroyed living organisms, but were not instrumental in combating toxins or in manufacturing antitoxins which he thought were produced by the lymphocyte. Or let us consider a modification of Bunting's theory, namely, that the micro- and macrophages merely break down formed antigen and thus prepare it for proper utilization by the lymphocyte or similar cells which can take up only dissolved material. If these or similar views were correct, the results of the blockade experiments could be interpreted differently. They could mean that blocked reticulo-endothelium could not prepare formed antigen for proper utilization by the antibody-forming cell. They could signify as well that the stimulated macrophages ingested and destroyed the antigen so rapidly[10] that its effective contact with the antibody forming cell was greatly reduced. That the latter explanation should be considered is borne out by recent experiences with so-called adjuvants, *i.e.*, oils which, when injected with the antigen, prolong antibody formation (Freund and Bonanto[11]). There is evidence to believe that this prolongation may be due to retention of antigen which, with the oil, is taken up by the macrophages and, because of the oil, is slowly broken down resulting in slow release and therefore more effective contact with the antibody-forming cell.

The other important argument in support of the reticulo-endothelial theory to be discussed here is the one which was recently advanced by Sabin.[12] Using a dye-protein, this author noted that after phagocytosis by the macrophage some of the dye was removed from each dye-protein aggregate, and after removal of the dye the protein particles were no longer visible. This was interpreted to mean "that the protein has been rendered into soluble form and passed into the cytoplasm." She further noted shedding of cytoplasm by the macrophage, which was "coincident with the time when the dye-protein is no longer visible within these cells, and when there are antibodies in the serum." This was believed to be an anatomical expression of synthesis of antibody within the cytoplasm of the macrophage and expulsion by the cell of the finished product.

Although Sabin's theory has attracted the attention of many investigators, it should be clear that the facts upon which it was based were not new and may be interpreted differently. It should be noted, for example, that she did not use the dye-protein in the soluble form in which it had been prepared; but that she first made an alum precipitate, the particles of which were large enough to be readily visible. She thus produced aggregates resembling bacteria or other formed antigens, which were so large that they had to be engulfed by the micro- and macrophages, and split by the enzymes of these cells before the original character of the antigen was regained.

The process observed by Sabin is obviously the same as the phagocytosis and digestion of gram-positive or acid-fast bacteria which, since the days of Metschnikoff, have been seen by numerous investigators. What was observed was splitting of raw material; the synthesis of antibodies within the phagocytic cell was not seen but merely deduced. It is equally possible that the products which were expelled from the cytoplasm of this cell were split products of the alum precipitate, rather than synthesized antibody.

The shedding of cytoplasm was stated to be a characteristic of macrophages. Such shedding has, however, been described and illustrated as a characteristic of lymphocytes[13] and of myeloblasts and promyelocytes.[14] It is generally known in thrombocytopoiesis.[15] Moreover: "It was striking that it was not these (macrophages showing digestion) that presented the shedding phenomenon but rather those without visible dye-protein particles."[12] Also: "It should be made clear that this process of shedding has not been observed within the living animal, but only in living cells removed from the animal. When the omentum or a drop of peritoneal fluid is first mounted on a slide, all the cells are rounded, but on standing for a short time the reaction of the shedding begins."[12] Similar phenomena are readily observed in supravital preparations of lymphocytes preceding their disintegration.

The relevance of this discussion is best shown by

9 C. H. Bunting, *Wisconsin Med. Jour.*, 24: 305, 1925.

10 C. H. Bunting, "The Polymorphonuclear Neutrophile Leucocyte." Handbook of Hematology, Vol. I. New York: Hoeber. 1938.

11 J. Freund and M. V. Bonanto, *Jour. Immunol.*, 48: 325, 1944.

12 F. R. Sabin, *Jour. Exp. Med.*, 70: 67, 1939.

13 H. Downey and F. Weidenreich, *Arch. Mikr. Anat.*, 80: 306, 1912.

14 R. Schuster, *Folia Haemat.*, 63: 382, 1940.

15 M. Watzka, *Zeitsch. Mikr. Anat. Forsch.*, 41: 498, 1937.

Sabin's rather casual observation that the dye-protein combination was engulfed and digested by the polymorphonuclear leucocytes as well as by the macrophages. But here the observed fact is interpreted in a different way: the granulocytes "play a role in bringing the antigen into the macrophages." This view will not be shared by many in the light of our knowledge of the numerous and vigorous enzyme systems contained in these cells.

We may say, then, that the observations of Sabin as well as the blockade experiments have added little to what was known to Metschnikoff 60 years ago. It has been merely shown once more that both the micro- and macrophages engulf and digest formed antigenic material and it has been revealed that proper blockade of the reticulo-endothelial system may interfere with this process. The products of digestion of the macrophage, however, have not been identified. Indeed, there is no evidence to show that the antibodies are products of this digestion.

THE LYMPHOCYTIC THEORY OF ANTIBODY FORMATION

Paralleling the reticulo-endothelial theory but obscured by it, a lymphocytic theory of antibody formation has long existed. Bunting[9, 10] has always maintained that antibodies are formed by the lymphocyte rather than the granulocyte or the macrophage. "The toxins (antigens) are apparently affixed by the lymphoid cells. If in great intensity the toxins cause necrosis of lymphocytes; if in proper dilution, one finds not necrosis, but stimulation and proliferation, with the production of antibodies. I realize that all will not agree with me that the lymphocytic series of cells produces the antibodies, yet all the pathological evidence I can obtain inclines me to that view."[9] That the polymorphonuclear leucocyte "does not play a part in antitoxic immunity seems to be indicated by a series of clinical observations which have been summarized in a general pathological law to the effect that no disease which runs its course with a neutrophil leucocytosis is followed by a lasting immunity."[10] Moreover, it was found that a high monocyte-lymphocyte ratio indicated susceptibility to tuberculosis, while a high lymphocyte-monocyte ratio suggested resistance.[16] "Considerable evidence both from infections in human patients and in animals suggest that the percentage of lymphocytes gives an index of the hosts' resistance, particularly in chronic diseases where a relative or absolute lymphocytosis is often associated with repair and recovery."[17]

These and similar clinical and pathological observations received experimental support first by Hektoen,[1] who showed that white rats exposed to x-rays revealed a decrease in hemolysin production, and that this was accompanied by a simultaneous reduction in the quantity of lymphatic tissue and bone marrow and in the number of circulating lymphocytes.

The observations of Hektoen were extended by Murphy and Sturm,[2] who exposed rabbits to x-rays of sufficient intensity to reduce the amount of their lymphoid tissue without damage to their bone marrow, and showed that a definite deficiency in the production of precipitins, bacterial agglutinins and protective antibodies resulted. On the other hand, rabbits which they subjected to an exposure of dry heat in amounts sufficient to increase the activity of the lymphatic tissue developed antibodies in larger quantity than did untreated animals. The effect of the x-rays on antibody formation could possibly be explained by blockage of the reticulo-endothelium, which was found to be engorged with the remains of lymphocytes. However, the response to heat could not be similarly explained because there was no evidence that dry heat had the slightest effect on macrophages.

Meanwhile, other facts were discovered which were difficult to reconcile with the reticulo-endothelial theory. It was observed, for instance, that after doses of staphylococcus vaccine large enough to stimulate marked proliferation of reticulo-endothelial elements the antibody titer remained low, whereas with small doses which did not produce visible proliferation of these cells high titers were obtained.[3] In the same experiments, the rise in antibody titer in the serum was found to parallel the activity of the Malpighian bodies of the spleen,[3] the cells of which were found to be lymphoid cells rather than histiocytes.[4]

The lymphocytic theory of antibody formation received new impetus through the experiments of McMaster and Hudack,[18] who showed conclusively that antibodies may be formed in lymph nodes. If two different antigens were injected, one into each ear of mice, the corresponding antibody appeared first in the lymph node of the same side. Fixation in the injected tissue or its regional lymph node as discussed by Menkin[19] was thus ruled out.

The observations of McMaster and Hudack were extended by our experiments[5] which showed that the cellular response within the lymph node during antibody formation is chiefly lymphocytic. The reticulo-endothelium in these experiments seemed to react independently. When antigens were injected into the pad of the hind foot of the rabbit, antibodies first appeared 2 to 4 days after the injection in the lymph

[16] C. A. Doan and F. R. Sabin, *Jour. Exp. Med.*, 52: 113, 1930.

[17] W. H. Taliaferro and C. Kluever, *Jour. Infect. Dis.*, 67: 121, 1940.

[18] P. D. McMaster and S. S. Hudack, *Jour. Exp. Med.*, 61: 783, 1935.

[19] V. Menkin, "Dynamics of Inflammation." New York: The Macmillan Company. 1940.

draining the popliteal lymph node (the only node regional to the site of injection). They reached their highest titer after six days. In all experiments it was found that the antibody titer was higher in the efferent lymph; in some cases the concentration was 100 times that found in the lymph of the afferent vessel. The production of antibody in the popliteal lymph node was preceded and accompanied by a rise in the output of lymphocytes in the efferent lymph which ranged from 15,000 to 20,000 per cu.mm. to 60,000 to 80,000 per cu.mm. or more. At the same time hyperplasia of the lymphatic tissue within the node occurred resulting in some experiments in a weight increase of the node from 0.2 gm to 1.0 gm or more. These observations lent little support to the idea that antibodies are direct products of reticulo-endothelial cells. The latter concept, in fact, is hardly consistent with the complex chain of events in the lymph node during the formation of antibodies as we have described it.

In a recent paper[6] we now have shown that, during antibody formation in the popliteal lymph node of rabbits, the lymphocytes in the efferent lymph vessels contain antibodies in a much higher concentration than the surrounding lymph. The ratio of titers amounted to from 8 to 16 in many instances. This observation seems to offer only two possible interpretations, that the lymphocyte either absorbs or adsorbs, or produces antibodies. Various *in vivo* and *in vitro* experiments[6] failed to show absorption or adsorption of antibody by the lymphocyte; nor was this idea supported by the observations of McMaster and Hudack[18] or our previous experiments.[5] On the other hand, it was noted that the ratio between lymphocyte titer and lymph plasma titer was greatest on the fifth day of the experiment, which was the time of greatest rate of antibody formation in the lymph node. The average ratios of titers fell from 7 on the fifth day to 2.3 on the seventh day, in sheep erythrocyte experiments, and from 5 on the fifth day to 3 on the seventh day, in typhoid vaccine experiments. This observation is consistent with a primary appearance of antibodies within, or on the surface of, the lymphocyte, and inconsistent with what would be expected if absorption or adsorption took place.

It is true that the lymphocyte is a somewhat prosaic cell with no particularly striking morphologic characteristics. If stained with routine stains, the cytoplasm seems to be singularly undifferentiated and unspecialized, especially when compared with that of the other white cells of the blood.[20] However, when studied while living it shows many interesting features, among which the refractile bodies of Gall[21] are the most intriguing. Moreover, lymphocytes contain a wealth of enzyme systems, which have been recently discussed by Barnes.[22]

It is also true that the lymphocyte does not phagocytose and therefore can not absorb corpuscular matter. But who can deny that it has the faculty of absorbing or adsorbing dissolved antigens or split products of particulate antigenic substances? In fact, if our reasoning is correct, the lymphocyte goes into action only after the raw material, *i.e.*, bacteria or other formed antigens, have been properly prepared by the action of micro- or macrophages. It seems that the polymorphonuclear leucocyte and the macrophage as well as the lymphocyte may be instrumental in antibody production. It may be through the cooperation of all these elements that antibodies are produced. If this concept is correct, it becomes clear why blockage of the reticulo-endothelial system may or may not interfere with antibody formation. It is also obvious why the destruction of lymphocytes by x-ray produces a reduction in antibody formation and why the stimulation of lymphocytopoiesis by dry heat induces an increase.

SUMMARY AND CONCLUSIONS

An attempt has been made to show that facts previously regarded as evidence for the reticulo-endothelial theory of antibody formation may be interpreted differently. Moreover, there are recent observations which are difficult to reconcile, if not inconsistent, with this pattern. However, the new observations as well as the old facts seem to fit into another theory of antibody formation in which the lymphocyte and possibly the granulocyte as well as the macrophage play an essential role. This theory is consistent also with the present concepts of the chemical reactions involved in antibody formation.[23, 24]

OBITUARY

CHARLES LE ROY GIBSON

CHARLES LE ROY GIBSON, associate professor of chemistry at the University of New Mexico, died at his home in Albuquerque on December 8, 1944.

Dr. Gibson was born at Clovis, New Mexico, on February 19, 1911, where his father was an official of the A. T. & S. F. Railway. He received his secondary education in the Belen, New Mexico, high school. During his high-school days, following a trip of the Belen high school football team, on which he

[20] C. K. Drinker and J. M. Yoffey, "Lymphatics, Lymph and Lymphoid Tissue." Cambridge: Harvard University Press. 1941.
[21] E. A. Gall, *Amer. Jour. Med. Sci.*, 191: 380, 1936.
[22] J. M. Barnes, *Brit. Jour. Exp. Path.*, 21: 264, 1940.
[23] S. Mudd, *Jour. Immunol.*, 23: 423, 1932.
[24] L. Pauling, D. H. Campbell and D. Pressman, *Physiol. Rev.*, 23: 203, 1943.

played, he was stricken with poliomyelitis from which he recovered, but which left him unable to walk except with the aid of crutches.

He entered the University of New Mexico in 1929, graduating with highest honors in 1933. After a year of teaching in a New Mexico high school, he became an assistant in chemistry at the University of New Mexico, and in nine years received repeated promotions, until at his death he was an associate professor. Studying during summer quarters and during a leave of absence, he earned the M.S. (1936) and the Ph.D. (1941) at the University of Colorado, his major work being in physical chemistry.

Dr. Gibson was rated by all his students and by his colleagues on the faculty as an exceptionally fine teacher. Not only was he very brilliant himself, but he possessed the faculty of making difficult academic subjects understandable to those less gifted. He commanded the respect and affection of every student who took his work. Shortly after Pearl Harbor, because of his ability in mathematics and physics, he was loaned by the chemistry department to teach physics in the pre-meteorology courses offered to army and navy students, for which work the university was signally commended by the Armed Forces.

In the anxious days following the entry of the United States into the war, Dr. Gibson worked constantly, taking his first vacation in several years, beginning July, 1944. The last of October he became seriously ill with malignant hypertension, from which he died on December 8.

Dr. Gibson is survived by his widow, Anna Vallevik Gibson, whom he married in August of 1944, and his mother, Mrs. Blanche Gibson, of Albuquerque.

Dr. Gibson was a member of the Kappa Sigma fraternity and the honor societies of Phi Kappa Phi, Sigma Xi and Phi Beta Kappa. He was also a member of the American Association for the Advancement of Science and the American Chemical Society.

JOHN D. CLARK

RECENT DEATHS

PROFESSOR WILLIAM TRELEASE, professor emeritus of botany of the University of Illinois, died at the age of eighty-seven years on January 2. He was director of Shaw's Botanical Garden, St. Louis, for twenty-three years before going to the University of Illinois in 1913.

DR. PAUL M. LINCOLN, from 1922 until his retirement in 1937 with the title emeritus director of the School of Electrical Engineering of Cornell University, died on December 20 at the age of seventy-four years.

DR. WILLIAM PINKERTON OTT, since 1924 head of the department of mathematics at the University of Alabama, died suddenly on December 25. He was sixty-eight years old.

DR. WILLIAM FRANKLIN LONG, director of the astronomical observatory of Franklin and Marshall College at Lancaster, Pa., a member of the faculty for twenty-six years, died on January 1 at the age of seventy-three years.

DR. GEORGE T. AVERY, professor of education at the Colorado State College of Agriculture and Mechanic Arts, formerly dean of the summer session and for the past two years director of training at the Joshya Hendy Iron Works, Sunnyvale, Calif., died suddenly on December 26 at the age of sixty-four years.

MISS LAURA M. LUNDIN, professor of physics and mathematics at Russell Sage College, Troy, N. Y., died on December 29 at the age of sixty-six years.

DR. JAMES O. RALLS, assistant professor of biological chemistry of the School of Medicine of the University of Buffalo, of which he had been a member of the staff for the last seventeen years, died on December 28.

SIR JOSEPH A. ARKWRIGHT, bacteriologist at the Lister Institute for Preventive Medicine, London, died on November 22 in his eighty-first year.

SCIENTIFIC EVENTS

GIFT TO THE UNIVERSITY OF CAMBRIDGE OF A COLLECTION OF SCIENTIFIC INSTRUMENTS AND BOOKS

AN exhibition of historic scientific instruments and books, presented by R. S. Whipple to the University of Cambridge, is described in *The Times*, London, as follows:

The collection is notable for its range and variety as well as its representative examples of fine craftsmanship from those centers in all countries where science flourished for nearly four centuries. Among astronomical instruments shown are astrolabes, nocturnals, and a remarkable collection of sundials of various shapes, sizes and materials by English and Continental makers from the sixteenth century onwards. Refracting and reflecting telescopes are well represented, and a feature of the exhibition is a Newtonian reflecting telescope in perfect condition made and used by Sir William Herschel, with 8-inch speculum mirror of 10-foot focal length, together with a finder telescope and a complete set of eye-pieces. The instrument was presented to the present collection for Cambridge by the late Howard Marryat.

The collection of microscopes contains examples of each important type from the times of Robert Hooke and Leeuwenhoek to the end of the last century and is a re

markable exhibit. Among other exhibits are numerous surveying, mathematical and physical instruments, scales and weights, and a case of miscellaneous optical instruments containing an ingenious walking-stick and umbrella complete with telescope, spy-glass, compass, microscope, thermometer and sundial, c. 1860. Among the 1,500 volumes of books are first editions of the works of Gilbert, Bacon, Galileo, Boyle, Hooke, Newton, Darwin and other scientific classics.

Mr. Whipple made the formal presentation of his collection to the university at a ceremony held in the Regent House on November 4 at which the vice-chancellor, who received the gift on behalf of the university, presided. The presentation was followed by the opening of the exhibition of the collection by Sir Henry Dale, O.M., president of the Royal Society. He emphasized the importance of the study of the history of science, not only by scientists who needed to appreciate the human side of their work, but also by those who read classics, history and theology. Sir Henry Dale said that he hoped that Cambridge would take steps to make the Whipple Collection the nucleus of a History of Science Museum and Library, which at first with a reader-curator and later a chair would become a vital center of university study and research.

THE TEXAS ACADEMY OF SCIENCE

THE Texas Academy of Science met in Galveston on November 9, 10 and 11, with the Medical Branch of the University of Texas as hosts. Over three hundred members were registered and all sessions were well attended. The sections on biology and medicine, geography and geology, conservation and the social sciences met at the same time as the junior and collegiate divisions that had their own programs.

There were eighty-eight papers on the program and several symposia. The general subjects of the symposia were: Conditions of Health on the Texas Coast Area (11 papers), Utilization of Natural Resources of the Coastal Area (8 papers) and Biology of the Cancer Cell (8 papers). Smaller groups covered processes of ageing in tissues and organs, international education and the geology of the coastal area. Two of the symposia will be published in the *Transactions* and the abstracts of all papers will be printed.

The evening sessions were of general interest and included an address on "Creative Engineering" by the retiring president, Professor W. H. Woolrich, dean of engineering at the University of Texas; "The Conservation of Human Resources," by Dr. Homer P. Rainey; "The Rise of Parícutin," by Professor F. M. Bullard, who has lived with the volcano for many months, and a color film of invertebrate life in the Gulf of Mexico as a prelude to the discussion of a biological station for this coast.

There were special exhibits of old and rare texts of medical history, scientific poetry, scientific illustration and two difficult physiological preparations.

The new officers will serve under the presidency of Dr. Walter P. Taylor, of College Station, Texas.

At the final business session, the academy took a strong stand for the betterment of scientific education in the secondary schools of Texas and also gave its support to academic freedom in higher education.

THE NEW HAMPSHIRE ACADEMY OF SCIENCE

THE twenty-fourth annual meeting of the New Hampshire Academy of Science was held in the Assembly Room of the New Hampshire Historical Society, Concord, N. H., on November 3 and 4, 1944.

At the Friday afternoon meeting, ten papers were presented by members, covering a wide range of scientific subjects. On Saturday morning two additional papers were presented, concluding the strictly scientific phase of the meeting.

On Friday evening, Mr. Jacob Freedman, of the Geological Survey, presented a lecture illustrated with kodachrome slides entitled "Alaska To-day." Mr. Freedman has but recently returned from his season's work in Alaska, where he carried on important geological investigations.

At the annual business meeting on Saturday morning, the secretary summarized the activities of the council since the last meeting of the academy at the University of New Hampshire in November, 1941. Earlier in 1944 the council had voted to recommend that the American Association for the Advancement of Science award their grant-in-aid to Miss Mabel Turner, of Antrim, to assist in defraying expenses in collecting and preparing herbarium specimens for her study on the flora of Hillsboro County, N. H. The council, earlier in 1944, had authorized also a second reprinting of one thousand copies of the popular Bulletin 1, "Geology of the Presidential Range," by Richard Goldthwait.

The following officers were elected for 1944–45: *President,* Professor Thomas G. Phillips, University of New Hampshire; *Vice-president,* William W. Bowen, Dartmouth College; *Secretary-Treasurer,* Professor A. R. Hodgdon, University of New Hampshire; *Member of the Council,* Professor Guy Williams, Colby Junior College, for a four-year term.

The final part of the program was the address of the retiring president, Professor Guy Williams, of Colby Junior College, which was entitled "Science in Post-War Education."

A. R. HODGDON,
Secretary-Treasurer

GRANTS OF THE SUGAR RESEARCH FOUNDATION

GRANTS have been made by the Sugar Research Foundation, New York City, to the following:

Dr. L. Emmett Holt, Jr., department of pediatrics, the Johns Hopkins University School of Medicine, Baltimore, for studies relating to synthesis of B vitamins by bacteria in the human intestinal tract, with special reference to the influence of various carbohydrates.

Dr. Andrew P. van Hook, department of physical chemistry, Lafayette College, for study of the kinetics of sucrose crystallization.

Dr. James M. Neill, department of bacteriology and immunology, Cornell University Medical College, New York, for investigation of traces of serologically active polysaccharides in sugar.

Dr. Curt P. Richter, psychobiologic laboratory, the Johns Hopkins University, for investigation of nutritive values of soft and raw sugars and of the carbohydrate-thiamine ratios taken by rats allowed free selection of all required nutrients.

Dr. John Haldi, department of physiology, School of Medicine, Emory University, for study of blood sugar levels in human subjects following high protein and high carbohydrate meals of isocaloric value.

Dr. William V. Cruess, chief, Fruit Products Division, Agricultural Experiment Station, University of California at Berkeley, for study of sugar in the quick freezing of fruit products.

Dr. Carl W. Borgmann, Engineering Experiment Station, University of Colorado, for pilot plant production of *d*-fructose (levulose) from sucrose and investigation of methods for separating dextrose and levulose.

These grants bring to more than a quarter of a million dollars the amount appropriated by the foundation during the year 1944.

SCIENTIFIC NOTES AND NEWS

THE presentation of the Perkin Medal[1] of the Society of Chemical Industry to Dr. Elmer K. Bolton, chemical director of E. I. du Pont de Nemours and Company, in recognition of "his outstanding accomplishments in the field of industrial research," took place on the evening of January 5. The medal was presented to him by Dr. Marston T. Bogert, professor emeritus of chemistry of Columbia University and senior past president of the society. In accepting the medal Dr. Bolton said: "I am deeply conscious of the fact that any credit for research accomplishments with which I have been connected belongs to the organizations of able research chemists with whom it has been my privilege to be associated. As their representative, I am happy to accept this award because, in honoring me, you honor them." Dr. Norman A. Shepard, chairman of the American section of the society, presided at the dinner. Dr. C. M. A. Stine, a vice-president of the du Pont Company, who was awarded the Perkin Medal in 1940, discussed Dr. Bolton's professional accomplishments, and Lammot du Pont, chairman of the board, spoke of the personal side of Dr. Bolton's career.

THE presidents of the Royal Society and of the Royal College of Physicians have awarded the Conway Evans Prize to Sir Thomas Lewis, F.R.S., "for his great contributions to medical knowledge on the working of the heart and circulation." This prize is given from time to time for scientific work of outstanding distinction and this is only the fourth occasion of its award since it was endowed in 1925 in accordance with the will of the late Dr. Conway Evans. Previous recipients of the prize are Sir Charles Sherrington (1927), the late Dr. J. B. S. Haldane (1933) and Sir Gowland Hopkins (1938).

[1] SCIENCE, December 1, 1944, p. 491.

THE Buckston-Browne Prize for 1944 of the Harveian Society of London, for an essay on the uses and abuse of sulphonamides, has been awarded to Dr. A. C. Frazer, professor of pharmacology at the University of Birmingham.

DR. EDWARD W. BERRY, professor emeritus of paleontology of the Johns Hopkins University, has been elected for 1945 president of the Geological Society of America.

DR. J. SHELTON HORSLEY, surgeon-in-charge of St. Elizabeth's Hospital, Richmond, Va., has been elected a corresponding fellow of the Medical Society of London. This society was founded by John Coakley Lettsom in 1773. It is the oldest institution of its kind in England. Dr. Horsley, who last May was awarded an honorary degree of doctor of science from the Medical College of Virginia, has been president of the Virginia Academy of Science, the Southern Medical Association, the Medical Society of Virginia and the Richmond Academy of Medicine.

OFFICERS for the current year of the Oregon Academy of Science are J. S. McGrath, *President;* Stanley Jewett, *President-elect;* A. L. Strand, *Past-president;* R. R. Huestis, *Treasurer,* and F. A. Gilfillan, *Secretary.* Other members of the council are J. A. Macnab and G. V. Copson, *biology;* E. G. Locke and Joseph Schulein, *chemistry,* and Warren D. Smith and I. S. Allison, *geology and geography.* The third annual meeting of the academy will be held in the Public

Library Building, Portland, Ore., on January 13. In addition to a general program, there will be section meetings in biology, geology and geography, and chemistry.

THE Institute of Medicine of Chicago has elected the following officers for 1945: *Honorary Chairman of the Board of Governors,* Dr. Ludvig Hektoen; *Chairman of the Board of Governors,* Dr. William F. Petersen; *President,* Dr. William C. Danforth; *Vice-president,* Dr. Daniel J. Glomset; *Secretary,* Dr. George H. Coleman; *Treasurer,* Dr. Grant H. Laing, and *Chairman, Committee on Admissions,* Dr. Bowman C. Crowell. Dr. Selim W. McArthur has been elected a member of the Board of Governors for a term of five years.

OFFICERS elected at the annual meeting held in New York on December 16 of the Association for Research in Nervous and Mental Disease are *President,* William G. Lennox; *Vice-presidents,* H. Houston Merritt and Wilder Penfield, and *Secretary-Treasurer,* Thomas E. Bamford, Jr. It was voted to center the program for the meeting a year hence on the subject of epilepsy and convulsive disorders.

DR. EDWARD C. ELLIOTT, president of Purdue University since 1922, will retire under the age limit on June 30.

DR. LAWRENCE W. DURRELL, head of the department of botany and plant pathology of Colorado State College of Agriculture and Mechanic Arts, has been appointed dean of the Science Division. The appointment is to take effect on July 1. Junius L. Forsberg, assistant professor of botany and plant pathology, will become research pathologist for the Illinois Natural History Survey at Urbana, Ill.

AT Columbia University, Dr. Robert C. Darling has been appointed associate professor of medicine; Alfred Gellhorn, of the Carnegie Institution of Washington, assistant professor of pharmacology, and David Weinman, of the Harvard School of Public Health, assistant professor of parasitology.

DR. LYLE R. DAWSON, professor of chemistry on leave from the Louisiana Polytechnic Institute, has become head of the department of chemistry of the University of Kentucky, succeeding Dr. L. L. Quill. For the last year Dr. Dawson has been the supervisor of a group of chemists in war research work in the metallurgical laboratory of the University of Chicago.

THE University of Chicago has made the following changes in the administration of the Division of the Biological Sciences, which includes the School of Medicine. Dr. R. W. Harrison, professor of bacteriology in the Walter G. Zoller Memorial Dental Clinic and the department of bacteriology and parasitology, has been appointed dean. Dr. A. C. Bachmeyer continues to be associate dean and director of the University Clinics. Until 1946, however, he will spend part of his time as director of study for the Commission on Hospital Care. Dr. Thomas Park, associate professor of zoology, has been appointed associate dean. The former dean, Dr. William H. Taliaferro, Eliakim Hastings Moore distinguished service professor of parasitology, has been appointed adviser to the president in the biological sciences. He continues to serve as chairman of the department of bacteriology and parasitology. Dr. B. C. H. Harvey, formerly dean of students in the Division of Biological Sciences and acting dean of students during the past year, has retired, and Dr. F. J. Mullin, assistant professor of physiology, has been appointed assistant dean of students.

DR. HENRY CLIFFORD DARBY, fellow of King's College, Cambridge, and lecturer in the department of geography of the university, has been appointed to the John Rankin Chair of Geography.

DR. R. G. D. ALLEN, British director of statistics of the Combined Production and Resources Board at Washington, who has been in the United States on government service since 1940, has been appointed to the chair of statistics at the University of London.

HENRY W. NICHOLS, chief curator of the department of geology of the Chicago Natural History Museum, retired on account of ill health on December 31, after serving for fifty years. Mr. Nichols, who is in his seventy-eighth year, joined the staff in 1894 as curator of economic geology. From 1897 to 1921 he was assistant curator of geology; from 1921 to 1933, associate curator; from 1933 to 1936 curator of geology, and from 1936 chief curator. He has conducted sixteen expeditions in North and South America for the museum, collecting a wide variety of geological material. Dr. Paul O. McGrew has been appointed acting chief curator of the department.

AT the National Bureau of Standards, Dr. Curtis J. Humphreys has been appointed chief of the section of radiometry of the Optics Division, in succession to Dr. William W. Coblentz, who retired on November 30 after serving for nearly forty years.

F. WAGNER SCHLESINGER, director of the Fels Planetarium in Philadelphia, has been appointed director of the Adler Planetarium in Chicago.

WALDO E. SMITH, who has recently been engaged in hydrological work with the Public Roads Administration, Washington, D. C., has been appointed to the newly established position of executive secretary of the American Geophysical Union.

Nature reports that the Secretary of the Department of Scientific and Industrial Research has made the following appointments at the British National Physical Laboratory: W. F. Higgins, secretary of the laboratory, has been appointed superintendent of the Division of Physics following a considerable period after the death of the late Dr. G. W. C. Kaye, in which he has been acting in that capacity; Dr. G. A. Hankins has been promoted to the superintendency of the Engineering Division of the laboratory to fill the vacancy caused by the resignation of Dr. S. L. Smith; E. S. Hiscocks, of the Raw Materials Department, Ministry of Supply, and previously of the Department of the Government Chemist, has been appointed secretary of the laboratory in succession to W. F. Higgins.

AFTER nearly two years in China, Dr. Joseph Needham, director of the British Council Cultural Scientific Office in China, has returned to Great Britain for consultations. He will go back to China early this year.

DR. A. G. H. SMART, medical adviser to the Secretary of State for the British Colonies, has been appointed representative of the United Kingdom on the Far Eastern Subcommittee on Health of the UNRRA.

DR. JACQUES ROUSSEAU has become director of the Montreal Botanical Garden to succeed Professor Marie-Victorin, who was accidentally killed last summer.

DR. G. M. SCHWARTZ, professor of economic geology at the University of Minnesota, has been on leave since June 15 for an investigation of various types of copper deposits for the U. S. Geological Survey. He has spent most of the time in Colorado and Arizona directing the exploratory work on porphyry ores. He returns to the University of Minnesota this month.

LECTURES are announced by the Chapter of the Society of Sigma Xi of Louisiana State University: On March 3 by Dr. G. W. Beadle, professor of biology at Stanford University; on March 19 by the Reverend Dr. James B. Macelwane, director of the Institute of Geophysics of St. Louis University, and on April 5 by Dr. Peyton Rous, member of the Rockefeller Institute for Medical Research.

COLONEL RICHARD P. STRONG, director of tropical medicine at the Army Medical School, Washington, D. C., delivered a lecture entitled "The Importance of Ecological Investigations in Tropical Medicine in the Present War" before the annual meeting on December 16 at San Juan of the Medical Association of Puerto Rico.

IT is announced that requests to the Committee on Research in Endocrinology of the National Research Council for aid during the fiscal period from July 1, 1945, to June 30, 1946, will be received until February 28. Application blanks may be obtained by addressing the Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the committee desires information regarding the proposed method of attack, the institutional support of the investigation and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses. Applications for aid in endocrine research on problems of sex in the narrower sense can not be given favorable consideration, but the committee will consider the support of studies on the effects of sex hormones on non-sexual functions—*e.g.*, on metabolism.

THROUGH a grant from the Rockefeller Foundation there have been established at the Cornell University Medical College and The New York Hospital "The J. Whitridge Williams Assistantships in Obstetrics and Gynecology," specifically designed for post-war training of a selective group that military service has deprived of advanced training comparable to that possible in the pre-war period. Lieutenant William F. Finn, U.S.A., M.C., has been awarded one of these assistantships.

A GIFT of $100,000 for a new building for the College of Pharmacy of Drake University, Des Moines, Iowa, has been made by the F. W. Fitch Company in recognition of the need for better facilities for training in the profession of pharmacy. The building will be constructed as soon as possible after material and labor are available and wartime restrictions permit.

DISCUSSION

SCURVY IN THE PARRY EXPEDITION OF 1819[1]

THAT tensile strength of surgical wounds is influenced adversely by the degree of vitamin C deficiency has been well established experimentally by Lanman and Ingalls[2] and others. Empirical observations to the same effect had been made in Hamilton's "Surgery" in 1865.[3]

The earliest recorded detailed clinical observation of impairment of wound healing in scorbutic patients, we believe, is in the "Journal of a Voyage for Dis-

[1] W. E. Parry, "Journal of a Voyage for the Discovery of a Northwest Passage," London, 1821.

[2] T. H. Lanman and T. H. Ingalls, *Ann. Surg.*, 105: 616, 1937.

[3] A. J. Lorenz, *Jour. Am. Diet. Assn.*, 20: 7, 432, 1944.

covery of a Northwest Passage" published in London in 1821. It is the report of the Polar Expedition of the *Hecla* and *Griper,* sent out by the British Admiralty and Board of Longitude in 1819–20 under command of Lieutenant William Edward Parry, R.N., F.R.S. Three surgeons, Drs. John Edwards, chief, Alexander Fisher and Charles James Beverly, assistant surgeons, accompanied the expedition and were placed in full charge of the food and sanitation as well as medical supplies of the two ships.

Recorded in the *Hecla's* log on Thursday, November 18, 1819, six months after the expedition had set sail from England:

About this time our medical gentlemen began to remark the extreme difficulty with which sores of every kind healed.

Again on February 7, 1820, this entry by Lieutenant Parry is found:

As we were now, however, approaching the coldest part of the season, it became more essential than ever to use the utmost caution in allowing the men to remain for any length of time in the open air, on account of the injury to their general health, which was likely to result from the inactivity requisite to the cure of some of the most trifling frost-bites. Mr. Edwards has favoured me with the following brief account of such cases of this nature as occurred on board the *Hecla*:—

"The majority of the men who came into the sick-list in consequence of frost-injuries during the severity of the winter, suffered mostly in their feet and especially in their great toes;—few cures were effected without the loss of the nail and cuticle in which the vital power was invariably destroyed. The exfoliation of these dead parts was always slow, and often attended with small ulcerations at the extremity of the toe."

Two months before, the lemon juice ration had been reduced to ⅔ of an ounce per man per day as a result of an accident to the expedition's major supply of bottled lemon juice. Ample antiscorbutic provision for the estimated two-year expedition had been made before setting sail.

My volume of Lieutenant Parry's *Journal,* which I fail to find listed in Hess's "Scurvy, Past and Present" or in any other bibliographies on historical records of scurvy, also contains a separate report by the ship's surgeons on the "State of Health and Disease of the Voyage."

Prefacing an autopsy report on the only fatality of the expedition, Surgeon Edwards states:

A solitary case of diseased lungs occurred during this voyage, which, in its progress, was combined with scorbutic symptoms.

Since clear-cut autopsy reports on scorbutic subjects are relatively rare in the earlier literature, a more detailed account will be presented by the writer in a contemplated paper reviewing other aspects of this expedition.

A. J. LORENZ,
Director, Nutrition Research
CALIFORNIA FRUIT GROWERS EXCHANGE,
LOS ANGELES

PURE SCIENCE

SUPPLEMENTING John M. Pearson's criticism[1] of Alexander W. Stern's note, "The Threat to Pure Science,"[2] since all sciences, apart from abstract mathematics, deal with material units of varying degrees of complexity in structure and behavior, does it not savor of priggishness to assume that "pure" sciences have a separate existence? The sciences constitute a vast interrelated mass of orderly arranged knowledge of natural phenomena, and it is high time that we should break down fictitious, pedagogical barriers separating them.

Beginning with recorded observations of the heavenly bodies, the science of astronomy recognized mathematically expressed "laws" (Kepler), an explanation of these laws with the aid of the newly developed calculus (Newton), and certain deviations from them (Einstein), based on the application of the recognized philosophical principle that all knowledge is relative, including even physical measurements. In 1868, Lockyer discovered helium in the sun with the aid of the spectroscope, but not until 1895 did Ramsay isolate it on earth from the mineral clevite; and modern astronomy leans heavily on physics and chemistry. From ancient times, astronomical knowledge served to guide travelers on land and sea; the invention of the chronometer by the mechanician, John Harrison, of the gyroscope compass by Elmer Sperry and the calculation of the "Ephemeris" are among the many gifts of other sciences to the science and art of navigation. Where does "pure" astronomy begin and end? Physics is learning from it of states of matter not yet producible by man.

Mr. Stern, a physicist, seems opposed to "professionalization." In physics, he says, this "will completely destroy freedom in science." In medicine, "the great majority of practitioners, being professional men, have neither time nor inclination to engage in research. Furthermore, as professional men they have no interest in pure science. Not until a scientific discovery or advance has gotten to the stage where they can use it, does it concern them. And then they are only concerned with its use and not with the scientific principles involved."

While in most sciences basic and spectacular advances are scored by a few, the success of these pioneers is facilitated by the painstaking work of

[1] SCIENCE, No. 2604.
[2] SCIENCE, No. 2599.

many mute inglorious Miltons, and even by the work of other famous men. Dr. William Beaumont laid a basis of our understanding of digestion by his observations on Alexis St. Martin, who had a stomach fistula due to a wound. The astounding Leonardo da Vinci aided anatomy and physiology by his precise observations and drawings. Scientific principles emerged from attempts to understand and explain observations. There is usually a delay in their emergence, and they may be modified by later knowledge.

"Pure" science is no quintessence which can be sublimated from the mass of observed facts without destroying or garbling the truth. Most scientific "laws" have exceptions, and the duty of scientists is to take broader rather than narrower views, so as to understand the very real coherence of natural phenomena, whether the knowledge is immediately useful or not, and irrespective of the calling (business, trade, profession) of the observer or explainer. Mr. Stern should be proud to be a professional man, for this term is applied to the more learned callings (theology, law, medicine, physics, chemistry, engineering), where some form of diploma or license from a competent examining body is generally demanded to protect the public, employers and other professional men from imposters and incompetents. Scientists know how to gauge and to classify their diverse fellows, and do so successfully.

As I understand the views of the British Society for Freedom in Science, it opposes the domination of scientific thought and activities by any group, especially through legislation framed by well-meaning but unscientific, warped or incompetent politicians who would regiment scientists. Despite the assertion of Lord Stamp, men of science are often "on top" as well as "on tap." Donald Nelson is a chemist; so is James B. Conant, and so was Charles Eliot, his predecessor as president of Harvard. Karl T. Compton and R. A. Millikan are physicists. Antoine Lavoisier, Benjamin Franklin and Benjamin Thompson (Count Rumford) are examples of what scientists have done in the field of politics. Men tend to gravitate to the positions where they are most useful. The great and increasing importance of science is opening many doors to those scientifically trained, especially if their training has been broad and human.

JEROME ALEXANDER

NEW YORK, N. Y.

I SHOULD like to discuss briefly some of Dr. Pearson's comments on my paper, as it concerns the nature of science. At a time when there is some cause for apprehension concerning the future of science it is essential to know what it is we are talking about. Dr. Pearson states that "one would conclude that Mr. Stern considers that 'pure science' is only metaphysics and excludes experimental and perhaps even theoretical science, if it is useful." I would no more consider pure science to be metaphysics than Dr. Pearson would consider applied science to be applied metaphysics. But I do state that science has nothing to do with usefulness. A scientific theory may be verified in the laboratory and not put to use thereafter, and it would still be part of the accepted body of science. And then there is the science of astrophysics, or would Dr. Pearson call it metaphysics?

Dr. Pearson has also stated that "the nature of science is the very essence of the practical." Does he believe that the researches of Faraday and Maxwell would lose any of their scientific value if no use were made of them? Does the scientific validity of the Bohr-Heisenberg Uncertainty Principle depend ultimately on whether some gadget can be made embodying this principle? Will the experimentally established phenomena of the fissure of uranium become part of science only when it is taken out of the laboratory and its principles incorporated in some rocket bomb? On the contrary, there is some justification for the belief that the growing socialization of science involves serious dangers to it. One must be alert and guard against scientific research degenerating into rubber, oil, textile, military—research. Such routine industrial research would ultimately destroy the adventure that is science. Fundamental investigations such as on the nature of the elementary particles, the relationship between field and matter, relativity and the universe, the study of extremely high energy particles in cosmic rays, the question of the production of multiple showers in one elementary act—would recede to the background. The pure science of physics whose study gives us a deeper insight and understanding of the ultimate constituents of the universe—matter and energy—may disappear. The desire to get at the nature of things would give place to the desire to make "better things." Thus, the age of scientific enlightenment and culture may be succeeded by an age of technology, where comfort replaces culture, and mankind replaces man. Science must be kept free, not because of the material comforts and riches it will bring us—that technology can do—but for the very preservation of our civilization.

ALEXANDER W. STERN

BROOKLYN, N. Y.

CEMENTING SINO-AMERICAN FRIENDSHIP

IN July, 1942, I published in SCIENCE under this same title the suggestion that scientists save unwanted reprints for eventual use in rehabilitating destroyed Chinese libraries after the war. The next month in the same periodical Wayne M. Hartwell, executive assistant to the Committee on Aid to Libraries in War Areas of the American Library Association, offered to

assist in caring for reprint material dedicated to this use which the donors were themselves unable to store until after the war. This committee is especially concerned with the receipt of full and partial sets of periodical literature for all war-torn libraries, but is in full accord with my suggestion concerning the saving of unwanted reprint material, especially for Chinese libraries. Several organizations and many individuals are working toward this same general objective of anticipating the needs for reconstruction of libraries in the devastated areas. The greatest obstacles in their programs seem to be the lack of present storage space and of personnel to handle the accumulating material. These difficulties are slowly being overcome, but as yet there are only limited facilities for receiving material, except where the donor is faced with the choice of turning it in for the post-war reconstruction program or for the current waste paper collection. It is, however, hoped that there will soon be an extensive drive for literature for this purpose, and it is in this connection and with the approval of the present executive assistant, Dorothy J. Comins, of the above named committee of the American Library Association with offices at the Library of Congress, and of Charles H. Brown, the chairman of their Committee on the Orient and Southwest Pacific, that I am issuing this reminder of the need for saving reprint literature.

Daily reports of bombing, burning and looting on the far-flung battle-fronts give strength to our worst fears of wide-spread destruction of valuable libraries. Thus the future demand for reprints, both currently appearing and of earlier date, is sure to be urgent and all should anticipate the need. Besides the demands from war-destroyed libraries we may justly anticipate the similar needs of new institutions which are being established and which will be built after the war with an ever-increasing crescendo as a result of the wartime stimulus toward scientific development. Although current scientific and technical periodicals are being purchased and laid aside for the reconstruction program, it is impossible to provide for all needs even in the near future. Hence, some destroyed libraries will welcome reprint material to represent the serials of which they will be unable to obtain full sets. Of course one should not confine one's efforts to saving only reprint literature, for all worthy periodicals and separate books will be needed. Broken sets of serials, and those which have been partially mutilated by removal of articles of special interest, can be used in completing other partial sets. Reprints are often considered by their owners as so specialized that, unless they are of immediate interest, they may as well be thrown away. A comprehensive program of collecting and distributing literature, such as is projected, will lead to their eventual arrival where they can be of value. Hence scientists should continue to save their unwanted literature for the peace-time reconstruction of war-torn libraries until they can be gathered together and properly handled in a coordinated program.

EGBERT H. WALKER
SMITHSONIAN INSTITUTION

AMERICAN SOCIETY OF PARASITOLOGISTS

THE report of the meeting of the Cleveland meeting of the American Association for the Advancement of Science which was published in the October 27 issue of SCIENCE erroneously stated (page 270) that the American Society of Parasitologists canceled its entire meeting. The society canceled its sessions at which general papers were scheduled to be read, but continued with its symposium on "Parasitology in Relation to the War" which it held jointly with the American Society of Zoologists and the Section on Medical Sciences. The program of this symposium is given in full in the report of the Cleveland meeting.

Following the symposium, the American Society of Parasitologists held a general business meeting, at which Asa C. Chandler, Rice Institute, was elected president for the year 1945 and Donald L. Augustine, Harvard University, was elected vice-president for the same term.

F. R. MOULTON,
Permanent Secretary

SCIENTIFIC BOOKS

TABLES OF BESSEL FUNCTIONS

A Guide to Tables of Bessel Functions. By HARRY BATEMAN and RAYMOND CLARE ARCHIBALD. Vol. 1, No. 7, July, 1944. 104 pp. of *Mathematical Tables and Other Aids to Computation,* published by the National Research Council, 2101 Constitution Ave., Washington, D. C. Special Number, $1.75.

BEGINNING in January, 1943, the National Research Council started the publication of a quarterly journal edited by the Committee on Mathematical Tables and Other Aids to Computation. This publication is intended as a clearing house for information concerning mathematical tables and other computational aids in the wide range of book, pamphlet and periodical literature. Its scope includes not only the field of pure mathematics, but also such fields as astronomy, chemistry, engineering, geodesy, geology, physics, physiology, economics, psychology and other scientific disciplines.

Eight numbers of the journal have been published—January, 1943, to October, 1944. The articles have included "Tables of Trigonometric Functions in Non-Sexagesimal Arguments," "Tables of Certain Functions in Dynamics of Structures," "Mathematical Tables in Reports of the B. A. A. S.," "Notes on the Computation of the Bessel Function $I_n(x)$," "Mathematical Tables in *Philosophical Magazine*," "Optimum-interval Punched-card Tables" and "Numerical Testing of Series by Calculations to Many Places of Decimals." Under the heading "Recent Mathematical Publications," 94 detailed reviews have been published. Under "Mathematical Tables—Errata," 53 contributions; under the important heading "Unpublished Mathematical Tables," 28; "Mechanical Aids to Computation," 11; "Notes," 25; "Queries," 10; and "Queries—Replies," 11.

Since the committee felt that at the present time hardly any publication of the kind could be more important than "A Guide to Tables of Bessel Functions," an entire number of the quarterly was devoted to this. The report is divided into two parts, the first consisting of a "Guide to Tables and Graphs; Polynomial Approximations and Asymptotic Expansions" and the second to a "Bibliography of Authors of Tables and Graphs." The first part is divided into 13 sections which lists under various headings the known tables and graphs together with their authors and the ranges of approximation.

The remarkable character of this contribution and its usefulnes to science may be better understood from a more detailed description of its contents. But a preliminary word of explanation about the subject itself may prove helpful in this connection.

The term "Bessel functions" is applied to the solutions of the linear differential equation

$$x^2y'' + xy' + (x^2 - n^2)y = 0.$$

This equation is called *Bessel's equation* after F. W. Bessel (1784–1846), who, although anticipated in its discovery by more than half a century by L. Euler, was the first to give in 1824 a systematic description of the solutions and to compute brief tables of two of them.

Bessel functions rival in their wealth of application their cousins, the circular functions. This may be inferred from the fact that the first appearance of the functions was in connection with the vibrations of a stretched membrane and the second in the solution of Kepler's equation fundamental to the description of the motion of a planet about the sun. Since their discovery they have appeared in many applications, in the transmission of currents in electrical net-works, in problems of elasticity, in the flow of heat, the distribution of potential, the theory of diffraction, and even in problems as remote from their origins as mathematical economics.

With an increase in application, new forms of the solution of the basic equation and a variety of nomenclature for them were developed. In the early studies the Bessel function of first kind was denoted by $J_n(x)$. This function is that solution of the fundamental equation which is characterized by the fact that it is a power series which converges for all values of x, and has no singularities when n is a positive integer. But interest soon developed in the second independent solution of the equation. Although this solution was called the Bessel function of second kind, it was defined variously by different writers and numerous symbols were used in its designation. To-day the preferred symbol for this function is $Y_n(x)$ and such extensive tables have been computed for it that its selection as the normal form for the second solution seems assured. Bessel functions of third kind are formed from those of first and second kind by means of the relationships: $H_n^{(1)}(x) = J_n(x) + i\, Y_n(x)$, and $H_n^{(2)}(x) = J_n(x) - i\, Y_n(x)$. Since Bessel functions in their application are not limited to real values of the variable x, numerous other auxiliary functions were developed in the study of the Bessel functions of a complex variable. To enumerate these various forms would be tedious and unnecessary to our purpose. For this and other information the reader is referred to the work of their modern biographer, G. N. Watson, whose classical treatise on the subject has been recently reissued.

Most conspicuous among the properties of the Bessel functions which have interested applied workers one finds the distribution and numerical values of the zeros. This is readily seen from the many tables of them which have been computed and the numerous ingenious devices which have been developed for their approximation. In other studies interest has centered upon the values of the functions for large values of the variable x or of the parameter n.

The work of the authors of the "Guide" under review was to enumerate all the tables of the values of the Bessel functions, of their zeros and of other related functions, together with a description of the extent to which the calculations have been carried. This has been accomplished by means of a compact notation illustrated by the following item under the heading $J_0(x)$ and $J_1(x)$: 12 *D*, Meissel 1, $x = 0$ (.01) 15.5, which means that these functions have been tabulated by Meissel in his first paper listed in the Bibliography, and that the computations are to 12 decimal places over the range from 0 to 15.5 at intervals of .01.

Two features of the "Guide" which the authors regard as of special importance are "(1) the complete listing of every known Unpublished Table of Bessel

Functions now available for consultation; (2) the assembly of information regarding known Errors in the tables recorded." The extensive character of this work is readily seen from the fact that there are 282 references to tables and graphs of $J_n(x)$ alone, and for all the functions one finds a total of 1,071 references.

Another service which this work supplies is to help in attaining some uniformity in the symbolism of the functions. Each enumeration of tables is preceded by an extensive account of the functions tabulated, together with a standard notation for them and some description of their origins. Although symbolism has improved in recent years by the publication of such well-known tables as those of the British Association for the Advancement of Science, the present "Guide" has given considerable support to the problem by agreeing "as far as possible with (the symbolism) used by English writers."

One particularly useful part of the work is the concluding section devoted to a summary of the literature on "Polynomial Approximations and Asymptotic Expansions," which was entirely the contribution of Professor Bateman. Much of the modern development of asymptotic series arose out of problems presented by Bessel functions, as one may infer from the fact that the perfection of the powerful saddle-point method, or method of steepest descents, is a product of the study of these functions. Computers and other statistical workers will be especially indebted to this section of the work.

From this it may be inferred that science has received a very useful addition to its tools in the publication of this "Guide," and it should prove to be an indispensable addition to standard works on the subject of Bessel functions.

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RADIO COMMUNICATIONS

Fundamentals of Radio Communications. By AUSTIN R. FREY. xii + 393 pp. Illustrated. New York: Longmans, Green and Company, Inc. 1944. $4.00.

WITH the large number of well-written texts on the subject of electronics and related fields, an author assumes a considerable responsibility in adding to the list. The author of this book, however, has not just written another book but has made a real contribution in offering a work which will prove of great value, not only to the student who desires to make a serious study of the field, but also to the practical engineer who may not be sufficiently interested in radio communications to maintain a complete library on the subject. The writer of this book struck a very effective balance between writing a text which is sufficiently complete and rigorous to satisfy every one and, at the same time, kept the mathematical treatments on a basis which stressed the physics of the problem rather than the mathematical niceties.

Obviously, the most important application of electronics to-day is in radio communication and this book properly stresses that application. However, a number of subjects which are not as important in communication as in other electronic applications are discussed in sufficient detail to make this book a valuable addition to the library of those not specifically interested in communications.

The treatment of the various subjects follows fairly conventional lines. The first chapter, devoted to a very complete discussion of resonant circuits, is especially effective. The next few chapters deal with thermionic emission and introduction to an elementary mathematics of the triode. Voltage amplifiers are discussed and this subject is brought up to date by a good discussion of the most recent developments in the field of ultra high frequency applications. Power amplifiers are then covered in a rather conventional manner. The chapter on oscillators is another one which the author treated rather better than the average. Not only is the theory worked out in a decidedly satisfactory manner, but many of the minor details which are important to an engineer are discussed. Chapters on modulation, demodulation and R.F. transmission lines follow with some emphasis on the more recent work on frequency modulation.

The last chapter in the book dealing with radiation is again one of the most satisfactory chapters in the book. In a rather brief but most effectively written chapter, the subject of radiation and antennas is discussed. Obviously, this discussion would not enable an engineer to design an antenna system, but a thorough reading of this chapter should enable any one to understand the basic principles of the subject. Most treatments of this important subject are so beclouded with mathematics that the results can only be dug out with considerable difficulty. In this chapter, the author began with a really simple equation for the instantaneous magnetic field at a distance r from a conductor. This equation, which he wisely does not attempt to derive but to which he gives adequate reference, is the starting point for all the subsequent discussion. By comparatively simple mathematical manipulation, the radiation field from a dipole and the other type of radiators follows.

For the benefit of those who would use this book in teaching classes, each chapter is followed by a number of selected problems of moderate difficulty. The usefulness of these problems, however, would be considerably increased if answers to at least some of them would be provided.

The book, as a whole, is very well written and is a good example of fine expository writing. A minor criticism of the book is that the drawings are definitely

not up to standards which we have come to expect from modern technical books. Some of the lettering is not clearly legible in the reduced scale of the drawings. It is hoped that in later editions this defect can be corrected. A few well-selected photographs might also have enhanced the attractiveness of this book. In conclusion, it can be stated that "Fundamentals of Radio Communications" is a well-written book which should be found in the library of every one seriously working in the field of electronics.

JOSEPH RAZEK

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REPORTS

RECOMMENDATIONS OF THE INTERNATIONAL CONFERENCE ON PENICILLIN[1]

AN International Conference on Penicillin was called for the purpose, if possible, of establishing an International Standard for penicillin, and of setting the International Unit of penicillin in terms of this standard. Meetings were held in the apartments of the Royal Society, London, from October 16 to 19, with Sir Henry Dale in the chair. The conference succeeded in fulfilling its purpose, unanimous agreement being reached on all points. It is reported that the results achieved by various laboratories were remarkably concordant, and served as a foundation for the work of the conference. During the course of the deliberations, no essential point of disagreement arose, and eventually the following draft of resolutions was adopted.

In order to facilitate discussion the conference began by recognizing that the different penicillins known as I, II and III in Great Britain are respectively identical with those known as F, G and X in the United States. The recommendations of the conference are as follows:

(1) That, notwithstanding the existence of more than one penicillin, it is desirable and possible to select and adopt an International Penicillin Standard consisting of a specimen of the pure crystalline sodium salt of Penicillin II or G; and an International Penicillin Working Standard, the specific activity of which has been determined in relation to that of the International Standard.

(2) That the use of these Standard Preparations, for the time being, would meet the needs of practical standardization and render quantitative results obtained in different countries sufficiently comparable.

(3) That the offer of the representatives of the United States of America to prepare the material for the International Standard, from contributions generously supplied for the purpose by manufacturers in the United States and the United Kingdom be gratefully accepted, and that the individual contributions be brought into one solution and finally crystallized as one uniform preparation.

(4) That, with a view to the eventual replacement of this International Standard by a preparation of identical properties, the physical and chemical constants of the preparation now being adopted shall be accurately determined.

(5) That approximately 8 grams of the International Standard shall be prepared and a quantity regarded as adequate to satisfy international requirements shall be deposited with the Department of Biological Standards, the National Institute for Medical Research, Hampstead, London, N. W. 3, on behalf of the Health Organization of the League of Nations.

(6) That, on receipt at Hampstead, the International Standard shall be dispensed in suitable quantities into separate containers and after complete desiccation shall be sealed in these containers in pure dry nitrogen gas, by the method and technique hitherto adopted for other International Biological Standards and shall thereafter be maintained in cold storage pending supply to national control centers.

(7) That the International Penicillin Working Standard for general distribution shall, for the present, consist of a calcium salt of penicillin and that the offer of the Food and Drug Administration of the United States of America to supply such a preparation be gratefully accepted. As in the case of the International Standard, the International Penicillin Working Standard shall be deposited with the Department of Biological Standards, the National Institute for Medical Research, Hampstead, London, N. W. 3, on behalf of the Health Organization of the League of Nations. It shall be dispensed in suitable quantities, in the manner described above, and stored and distributed under the same conditions as other International Biological Standards.

(8) That the International Unit of Penicillin be defined as *the specific penicillin activity contained in 0.6 microgram of the International Penicillin Standard.*

The International Unit so defined is approximately equivalent to the unit originally adopted by Heatley and other collaborators of Florey (1941)[1] and commonly known as the "Oxford" unit.

(9) That 2.7 micrograms of the present International Penicillin Working Standard (see paragraph 7 above) be accepted as containing 1 International Unit of Penicillin.

(10) That for the determination, by a suitable method of comparative assay, of the specific activity of an unknown preparation of penicillin in terms of the International Standard it is necessary to use a suitable strain of *Staphylococcus aureus*, and that this strain must have practically equal sensitiveness to the inhibitory actions of Penicillin I, or F, and Penicillin II, or G. The two strains of *Staphylococcus aureus* which at present can be

[1] "Further Observations on Penicillin," Abraham, Chain, Fletcher, Florey, Gardner, Heatley, Jennings. *Lancet*, ii, p. 177, 1941.

certified, by the experience of many workers, to fulfill these conditions are those known variously as

(a) No. 6571 of the National Collection of Type Cultures (England).
No. NRRL B-314 (Northern Regional Research Laboratory, Peoria, Illinois, U. S. A.).
No. 9144 of the American Type Culture Collection (Washington, D. C., U. S. A.).
and (b) No. 209-P, the Food and Drug Administration (Washington, D. C., U. S. A.).
No. NRRL B-313 (Northern Regional Research Laboratory, Peoria, Illinois, U. S. A.).
No. 6538 of the American Type Culture Collection, Washington, D. C., U. S. A.).

Both of these cultures may be obtained by application to the National Collection of Type Cultures, The Lister Institute, London, or to the American Type Culture Collection, Georgetown University, Washington, D. C.

(11) That the Conference recognizes that it may eventually become necessary and practicable to establish further standards made from other varieties of Penicillin; and recommends that, with a view to such further development, efforts should be made to make pure samples of other penicillins available for international exchange among research workers in this field.

These recommendations are signed by M. V. Veldee, R. P. Herwick and R. D. Coghill, *chairman.*

SPECIAL ARTICLES

PYRIDOXAMINE AND THE SYNTHESIS OF AMINO ACIDS BY LACTOBACILLI

Lactobacillus delbrückii LD5 requires 15 amino acids, namely, leucine, isoleucine, valine, cystine, tryptophane, tyrosine, phenylalanine, glutamic acid, threonine, aspartic acid, lysine, arginine, serine, methionine and alanine, for full growth in a basal medium of essentially the same composition as that described for *Lactobacillus casei.*[1] Little or no growth occurs if any of these amino acids, with the exception of the last two, is omitted; approximately half-maximum growth is obtained in the absence of either methionine or alanine. Replacement of the pyridoxine of the medium by an equal amount (2 γ per 10 cc medium) of pyridoxamine (or pyridoxal)[2,3] eliminates the requirement of *L. delbrückii* for lysine, threonine and alanine but not for any of the remaining 12 amino acids. Good growth occurs in the absence of any one of these amino acids or of all three (Table 1). Similar results were obtained with *L.*

TABLE 1

INFLUENCE OF PYRIDOXINE AND PYRIDOXAMINE ON AMINO ACID REQUIREMENTS OF LACTOBACILLUS DELBRÜCKII LD5

Amino acids omitted from basal medium	*L. delbrückii* LD5		
	No pyridoxine	Pyridoxine*	Pyridoxamine
Lysine	1.0†	2.0	8.9
Threonine	0.9	1.2	7.7
Alanine	0.8	4.5	8.5
Lysine, threonine, alanine	1.0	1.4	6.0
None	1.0	8.5	8.9

* Seitz filtered.
† The figures are the cc of 0.1 N acid formed in 10 cc of medium during incubation for 72 hours at 37°; growth is proportional to acid formation.

casei and *L. arabinosus* 17–5. However, the amino acid requirements of *Streptococcus lactis* R, which includes lysine, threonine and alanine,[4] are not affected by pyridoxamine except that the latter supports a small amount of growth in the absence of alanine.

It was possible, therefore, to determine by means of *S. lactis* R whether lysine, threonine and alanine are synthesized by the lactobacilli when grown in media containing pyridoxamine. Cells of the three lactobacilli cultivated without lysine, threonine or alanine were hydrolyzed in sealed ampules with 10 per cent. HCl for 10 hours at 15 pounds pressure. Addition of portions of the neutralized cell hydrolysates to *S. lactis* media from which either lysine, threonine or alanine was omitted, permitted maximum growth of *S. lactis* indicating that all three amino acids were present in each lactobacillus.

Pyridoxamine fulfils functions other than those concerned with the formation of the three specified amino acids, since it is necessary for development of *L. delbrückii* and *L. casei* also in media containing those amino acids (Table 1). However, in such media, pyridoxine is equally effective. There are indications that pyridoxine is involved in protein[5] and tryptophane[6] metabolism in animals and that pyridoxine and pyridoxal function in the decarboxylation of tyrosine by *Streptococcus fecalis.*[7]

L. arabinosus differs from the other two lactobacilli in that it does not require added pyridoxine for development in an otherwise complete medium. Presumably it synthesizes pyridoxine or some similarly active compound, possibly pyridoxamine.[8] The necessity of adding the latter for growth of *L. arabinosus* in media lacking lysine, threonine and alanine may be

[1] Hutchings and Peterson, *Proc. Soc. Exp. Biol. Med.*, 52: 36, 1943.
[2] Snell, *Jour. Biol. Chem.*, 154: 313, 1944.
[3] Harris, Heyl and Folkers, *ibid.*, 154: 315, 1944. We are indebted to these investigators for supplies of the pyridoxine derivatives.
[4] Snell and Guirard, *Proc. Nat'l. Acad. Sci. (U. S.)*, 29: 66, 1943.
[5] McHenry and Gavin, *Jour. Biol. Chem.*, 138: 471, 1941.
[6] Lepkovsky, Roboz and Haagen-Smit, *ibid.*, 149: 195, 1943.
[7] Gunsalus and Bellamy, *Jour. Bact.*, 47: 413, 1944; *Jour. Biol. Chem.*, 155: 357, 1944.
[8] Bohonos, Hutchings and Peterson, *Jour. Bact.*, 44: 479, 1942.

due to synthesis of inadequate amounts of pyridoxamine. This is suggested by the fact that *L. casei* and *L. delbrückii* require ten times as much pyridoxamine for growth without the above three amino acids as with them.

An explanation is now available for the disagreement between investigators as to the essentiality of lysine and threonine for growth of *L. arabinosus*.[9] During heat sterilization of the medium sufficient pyridoxamine may be formed from the interaction of the pyridoxine and amino acids[2] to permit good growth of *L. arabinosus* in the absence of lysine or threonine. Autoclaving a medium deficient in lysine for 30 minutes instead of the customary 15 or 20 minutes permitted maximum growth, whereas the same medium autoclaved without pyridoxine and to which Seitz filtered pyridoxine was added, failed to support growth unless lysine was present.

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THE EFFECT OF UREA, URETHANE AND OTHER CARBAMATES ON BACTERIAL GROWTH[1, 2]

UREA has been shown to have anti-bacterial properties by Peju and Rajat[3] and Foulger and Foshay[4] and to be effective in the treatment of infected wounds and diphtheria carriers by Symmers and Kirk.[5] Holder and MacKay[6,7] and Ilefeld[8] have reported favorable response of infected wounds to treatment with mixtures of urea and sulfonamides. Tsuchiya, Tenenberg, Clark and Strakosch[9, 10, 11] have recently shown that urea inhibits para-aminobenzoic acid and methionine, substances which antagonize the action of the sulfonamides. These findings could not be confirmed by Kirby[12] but have been confirmed by Lee, Epstein and Foley.[13]

Urethane has received very little attention with respect to its action on bacterial growth but has been found to depress the respiratory rate of yeasts and, in low concentrations, to stimulate, and in larger amounts to depress the luminescence and respiration of the luminescent bacteria.[17, 18, 19] Johnson[14] has claimed that urethane exerts an anti-sulfonamide effect on luminous bacteria but McIlwain[15] and Martin and Fisher[16] using streptococci in *in vitro* and *in vivo* studies could not confirm this work.

The investigations reported here indicate that urea and urethane are both bacteriostatic and bactericidal for many organisms, that they antagonize slightly the sulfonamide inhibitors and that they increase the solubility and bacteriostatic activity of the sulfonamides. Urethane appears to be greatly superior to urea in all respects.

Six per cent. urea and 3 per cent. urethane were found to be bacteriostatic for *E. coli* in veal infusion broth containing 50 per cent. horse serum. *Staphylococcus aureus* required higher concentrations of either drug in the same medium to produce a similar effect; 4 per cent. urethane and 10–12 per cent. urea inhibited growth of this organism. The bacteriostatic levels of both drugs were found to be lower in synthetic media. The growth of *Pneumococcus,* hemolytic *Streptococcus, Proteus vulgaris, E. typhi, Pseudomonas pyocyaneus, S. schotmulleri* and *S. paradysenteriae* (Flexner) in serum-veal infusion medium was found to be inhibited by 2 per cent. urethane and 6 per cent. urea, these being the final concentrations of the drugs in the medium. Several strains of some of these bacteria were examined and all were found to react in the same manner.

Studies of the effect of other urea derivatives such as propyl and butyl carbamate on the same group of organisms showed that bacteriostasis is produced by lower concentrations than those necessary with either urea or urethane. One to 2 per cent. propyl carbamate and 0.5 to 0.75 per cent. butyl carbamate were found to inhibit the growth of all the organisms listed above.

In a large number of bactericidal tests in which the bacteria enumerated above were exposed to various concentrations of either urea or urethane at a temperature of 37° C. and subcultures taken at periodic intervals, it was found that killing occurred after 5 to 15 minutes of contact with 10 per cent. urethane in

[9] Hegsted, *Jour. Biol. Chem.*, 152: 193, 1944.

[1] From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

[2] Aided by a grant from the Johnson Research Foundation, New Brunswick, New Jersey.

[3] G. Peju and J. Rajat, *Compt. rend. Soc. de Biol.*, 61: 477, 1906.

[4] J. H. Foulger and L. Foshay, *Jour. Lab. and Clin. Med.*, 20: 1113, 1934–35.

[5] W. St. C. Symmers and T. S. Kirk, *Lancet*, 2: 1684, 1915.

[6] H. G. Holder and E. A. MacKay, *The Military Surgeon*, 90: 509, 1942.

[7] H. G. Holder and E. A. MacKay, *Surgery*, 13: 677, 1943.

[8] F. W. Ilefeld, *Surg., Gynec. and Obst.*, 76: 427, 1943.

[9] H. M. Tsuchiya, D. J. Tenenberg, W. G. Clark and E. A. Strakosch, *Proc. Soc. Exp. Biol. and Med.*, 50: 262, 1942.

[10] D. J. Tenenberg, H. M. Tsuchiya, W. G. Clark and E. A. Strakosch, *Proc. Soc. Exp. Biol. and Med.*, 51: 247, 1942.

[11] H. M. Tsuchiya, D. J. Tenenberg, E. A. Strakosch and W. G. Clark, *Proc. Soc. Exp. Biol. and Med.*, 51: 245.

[12] W. M. M. Kirby, *Proc. Soc. Exp. Biol. and Med.*, 53: 109, 1943.

[13] S. W. Lee, J. A. Epstein and E. J. Foley, *Proc. Soc. Exp. Biol. and Med.*, 54: 107, 243, 245, 1943.

[14] F. H. Johnson, SCIENCE, 95: 104, 1942.

[15] H. McIlwain, SCIENCE, 95: 509, 1942.

[16] G. J. Martin and C. V. Fischer, SCIENCE, 95: 603, 1942.

veal-serum broth even when inocula as large as 50,000 to 75,000 bacteria were used except with *Staphylococcus aureus* which, in some of the tests, was killed only after 3 to 4 hours of exposure; with small inocula of this organism bactericidal action was often noted in 30 minutes. With a concentration of 5 per cent. urethane the time required to produce bacterial death was appreciably longer than with the larger amount. The action of urea was found to be much weaker than that of urethane and 2 hours of contact were often required before 20 per cent. urea in broth produced the same degree of effect as did 10 per cent. urethane in 5 minutes. Twenty per cent. urea was found not to be bactericidal for *Staphylococcus aureus* even after exposure for 24 hours. *Pseudomonas pyocyaneus* and *Proteus vulgaris* appeared to be the most susceptible to the action of the carbamates.

The action of urea and urethane on para-aminobenzoic acid was examined a number of times using *E. coli* and *Staphylococcus aureus* in synthetic and horse serum-veal infusion media. The amounts of sulfanilamide used were 15 mgms per 100 cc in the synthetic and 75 mgms per 100 cc in the serum-veal infusion medium for *E. coli* and 50 mgms per 100 cc in synthetic and 100 mgms per 100 cc in infusion broth for the *Staphylococcus*. In one series of experiments two non-bacteriostatic amounts of urea (2 and 4 per cent.) and urethane (1 and 2 per cent.) were titrated against fourteen concentrations of para-aminobenzoic acid ranging from 0.001 to 2.5 mgms per 100 cc; in another, seven different quantities of para-aminobenzoic acid were tested against six varying amounts of urea. Both urea and urethane produced inhibition of the sulfonamide antagonist, the effect being evident, however, only with very small quantities of para-aminobenzoic acid. Inhibition of PABA by urea occurred for 96 hours only when 0.001 mgms per 100 cc of the acid were used. The carbamates antagonized slightly higher concentrations of PABA only for short periods of time, while larger amounts of this substance showed complete lack of inhibition by either urea or urethane. Urethane was more active than urea since about one half the concentration produced the same effect on PABA.

The combination of non-bacteriostatic amounts of urea and urethane with non-bacteriostatic quantities of sulfanilamide produced pronounced inhibition of bacterial growth. The bactericidal potency of urethane was also increased moderately by the addition of non-bactericidal concentrations of sulfathiazole. Non-bacteriostatic amounts of urea and urethane in combination with sulfanilamide produced marked flattening of the growth curves of *E. coli* and *Staphylococcus aureus*, each substance alone yielding a normal curve of bacterial multiplication.

It has been shown that urea increases the solubility of the sulfonamides. A similar effect was noted with urethane; thus, the solubility of sulfanilamide at 20° C. was 400 mgms per 100 cc in water and 1,000 mgms per 100 cc in 10 per cent. urethane solution in water. Two hundred mgms of sulfathiazole could be dissolved in 100 cc of 10 per cent. urethane in water, but only 69 mgms went into solution in water alone at 20° C.

The mode of action of urethane and urea on bacterial growth is not clear, but certain factors appear to have been ruled out. The osmotic pressure of the solutions probably plays no rôle since it has been found that concentrations of urea and urethane which inhibit bacterial growth have no effect on the human erythrocyte even after exposure for 24 hours at 37° C. Furthermore, while 10 per cent. urethane invariably kills all the organisms studied, 10 per cent. sodium chloride, 20 per cent. sucrose and 20 per cent. glucose solutions show no bactericidal action even after 24 hours at 37° C. All the solutions of the carbamates in the media in which the tests were carried out had a pH of from 7.2 to 7.4. Harvey[17] and others[18, 19] have shown that narcotics, among them urethane, have a depressant effect on the enzyme systems of luminescent bacteria in certain concentrations; it is possible that the same type of action is responsible for the effects noted in the studies reported here.

A small number of various types of infections in man have been treated with a mixture containing ten grams of urethane and 1 gram of sulfanilamide in 100 cc of water, and those in which Gram negative bacteria were the predominant organisms responded very rapidly with sterilization and healing of the wounds. Infections with Gram positive bacteria were much more refractory to treatment. Some evidence was also obtained which indicates that urethane does not impede wound healing in man.

The studies reported here indicate that urethane and urea exert both a bacteriostatic and bactericidal action (depending on the concentration used) mainly against Gram negative bacteria but also to a lesser degree against Gram positive organisms, that they antagonize sulfonamide inhibitors, increase the solubility of sulfonamide compounds, and are of value in the treatment of Gram negative infections in man. The activity of the four carbamate compounds tested against bacteria appears to be in the following order; most active is butyl carbamate and least effective urea, with urethane and propyl urea occupying a middle ground.

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ALICE MCDONALD

[17] E. N. Harvey, *Erg. d. Ensymforsch.*, 4: 365 (cited by Johnson), 1935.
[18] N. U. Medrum, *Biochem. Jour.*, 24: 1421, 1930.
[19] G. W. Taylor, *Jour. Cell. and Comp. Physiol.*, 4: 329, 1933–34.

THE INFLUENCE OF "FOLIC ACID" ON SPONTANEOUS BREAST CANCERS IN MICE[1]

IN a recent communication[2] we reported that a "folic acid concentrate" and a crystalline *L. casei* factor[3] ("folic acid") were found to be strong inhibitors of tumor growth.

In the following communication evidence for the therapeutic action of *L. casei* factor on spontaneous breast cancers in mice is presented. Further details will be given later.

Experimental: 149 mice from three different strains (Jackson Memorial Laboratory, strain A, Rockland strain and Bagg strain) bearing single spontaneous breast cancers were selected for the experiments. A definite diagnosis of malignancy was established by biopsy. The animals were kept on a normal diet (Rockland mouse pellets); 120 animals were divided into two groups (60 mice each) in such a way that they were matched as to strains and, as closely as possible, as to location and size of the tumors.

One of these groups of 60 mice received daily intravenous injections of 5 micrograms *L. casei* factor over a period of 4 to 6 weeks; the control group of 60 mice did not receive any injections. Another set of 29 mice were also treated with 5 micrograms of *L. casei* factor, but without "matched" controls. No toxic effect was observed in the treated animals.

Results are presented in Table 1.

TABLE 1

EFFECT OF L. CASEI FACTOR ON SPONTANEOUS BREAST CANCERS IN MICE

Number of mice	Dose injected	Number of healed mice	Number of living mice	Number of new tumors
60	5 micrograms	26	34	0
60	0	0	20	14
29	5 micrograms	12	15	1

It is evident from this table that intravenous injections of 5 micrograms of *L. casei* factor led to complete disappearance in 38 among 89 tumors. No tumor disappeared among the 60 controls. Fourteen controls developed new tumors, whereas one new tumor was observed among the treated mice. Among the 89 treated mice 49 are still living, including 33 healed animals.

The observation period extends from two to ten months for treated groups and controls. During this period, no local recurrences or new tumors were observed among the healed animals.

Summary: Complete regressions of spontaneous breast cancers in mice were observed in 38 among 89 animals (43 per cent.). The treatment consisted of daily intravenous injections of 5 micrograms of *L. casei* factor ("folic acid"). The treated animals lived longer than the controls, especially the healed mice. The incidence of the development of new tumors was decreased among the treated mice as compared with the controls.

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[1] This work was aided by grants of the International Cancer Research Foundation and the Lederle Laboratories, Inc.

[2] C. Leuchtenberger, R. Lewisohn, D. Laszlo and R. Leuchtenberger, *Proc. Soc. Exp. Biol. and Med.*, 55: 204, 1944.

[3] The *L. casei* factor was obtained through the courtesy of Dr. E. L. R. Stokstad and Dr. B. L. Hutchings, of the Lederle Laboratories, Inc.

PENICILLIN ASSAY[1]

IN SCIENCE for March 24, 1944, a method was given for determining the potency of penicillin.[2] The following is a further development and gives a simple statistical method of determining both the potency of antibiotic substances in terms of suitable standards and error of assay by use of a chart and a nomograph in conjunction with four figures obtained by certain additions and subtractions of the diameters of the zones of inhibition of the incubated plates.

The penicillin assay to which this statistical method applies directly involves four plates (Petri dishes) seeded with *Staph. aureus* or other appropriate organism. Four small glass cups are placed on each plate (metal cups or blotter discs may be used). The cups are then filled with penicillin so that each plate has two dilutions of the standard and two dilutions of the unknown made up so that one dilution contains .25 unit/ml and the other 1.00 unit/ml. The unknown is diluted according to its estimated potency. Thus the ratio of the two doses on both the standard and the unknown is 4 to 1 (or log of ratio of doses = log 4 = .602).

Both the formula for the potency as a per cent. of the standard and the formula for the ratio of the error of the potency to the potency have been graphed in relatively simple form for use in the laboratory[3] as shown in Figs. 1 and 2. To use the nomograph, simple additions and subtractions have to be made on the measurements of the diameters of the zones of inhibition to obtain V, W, R_s, and R_w.

[1] The author wishes to gratefully acknowledge the encouragement and assistance of Dr. W. Edwards Deming, of the Bureau of the Budget, and also the drafting of the chart and nomograph by Pete James, of the Food and Drug Administration.

[2] "A Rapid Quantitative Method for the Determination of Penicillin," M. B. Sherwood, E. A. Falco and E. J. deBeer, SCIENCE, 99: 247.

[3] Enlarged graphs and the procedure employed by the Food and Drug Administration in their routine assay of penicillin may be obtained by writing to the Division of Bacteriology of the Food and Drug Administration. Mathematical derivation of the method will be published elsewhere.

An example may clarify the procedure. The data are given in Table 1.

TABLE 1
PENICILLIN PLATE-ASSAY[4]

Plate No.	s_L .25 u/mg mm	s_H 1.0 u/mg mm	u_L estimated .25 u/mg mm	u_H estimated 1.0 u/mg mm	v or $(u_L+u_H)-(s_L+s_H)$	w or $(s_H+u_H)-(s_L+u_L)$
1	16.0	22.5	15.0	20.0	− 3.5	11.5
2	16.2	22.5	14.5	19.5	− 4.7	11.3
3	16.0	22.5	15.0	22.0	− 1.5	13.5
4	15.0	22.0	14.0	21.0	− 2.0	14.0
Sum	63.2	89.5	58.5	82.5	− 11.7 = V	50.3 = W
Range	...	...	...	...	3.2 = R_v	2.7 = R_w

[4] Data from the laboratories of the Division of Bacteriology, Food and Drug Administration.

The columns headed s_L, s_H, u_L, and u_H (diameters of zones of inhibition on low and high doses of standard and unknown) are totalled and the values of v and w are calculated. The values of V and W are checked by separately adding the columns headed v and w. R_v is the range of the v column. R_w is the range of the w column.

The graph shown in Fig. 1 is entered with $V = -11.7$

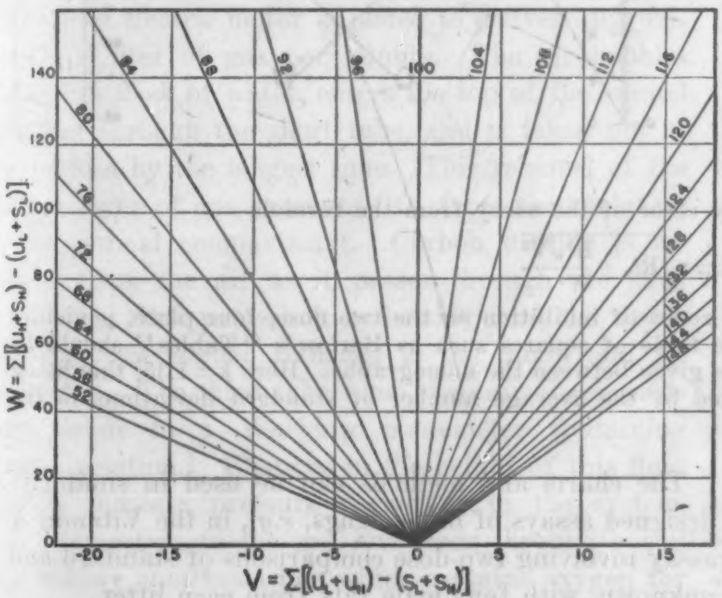

FIG. 1. Chart for determining potency as per cent. of a standard from the formula:

$$\text{Potency} = \text{antilog}\left(2 + \frac{.602V}{W}\right)$$

V and W are calculated from diameters of zones of inhibition. The chart is entered with coordinates V and W and the potency is read off the radial lines. The ratio of doses is 4: 1.

and $W = 50.3$ and the potency is found to be 72 per cent. of the standard.

To calculate the error of the assay, the inside scales on the right-hand side of the nomograph shown in Fig. 2 are entered with $V = 11.7$ and $W = 50.3$ (only absolute values of V, W, R_v and R_w are used in the calculation of the error of the assay). By means of a straightedge connecting first the values of V and W, marking the point of intersection of the straightedge and the diagonal line and then connecting this marked point and R_w, read the value of Q (.65). T is equal to $Q^2 + R^2_v = 10.66$. The left-hand side of Fig. 2 gives the value of the ratio of the error of the assay to the potency to be .087 by connecting the value of W (or 50.3) with the value of T (or 10.66). The error of the assay equals $.087 \times 72 = 6.3$.

However, if $11.4R_w$ is greater than W the slope of the assay does not differ significantly from zero by Student's *t* test. This is an indication of faulty procedure, and when the fault is located, the assay should be repeated. If the potency lies outside the limits given in Fig. 1, the assay should be repeated using a higher or lower dilution. In practice one may also wish to test the parallelism of the lines, however, lack of parallelism influences the size of the error of the assay.

The charts as given apply directly only to assays in which the ratio of the high dose to low dose equals 4 to 1. The potency chart can be used for any number of plates and should be remade for ratios of doses other than 4: 1, although the following formula gives an approximation within one per cent.:

$$\text{Corrected Potency minus } 100 = (\text{Potency from chart minus } 100)\frac{\text{log ratio of doses}}{.602}.$$

The nomograph for the error of the assay applies directly only if 4 plates are used. However, it can be used for any number of plates and any ratio of doses by multiplying the resultant ratio of the error of assay to the potency by the appropriate figure given in Table 2.

TABLE 2

Number of Plates N	Ratio of doses 4 : 1	Ratio of doses 3.16 : 1	Ratio of doses 2 : 1
2	1.2901	1.0715	.6451
3	1.0534	.8749	.5267
4	1.0000	.8306	.5000
5	.9896	.8219	.4949
6	.9949	.8263	.4974
7	1.0071	.8364	.5035
8	1.0226	.8493	.5113

The error of the assay calculated here or in any penicillin assay estimates only how closely one assayist can check himself on any given set of dilutions of unknown and standard. It does not include any errors of weighing or errors due to variations in materials or subdivisions of a lot of penicillin. Since very minute amounts of materials are used in this type of penicillin plate-assay, appreciable errors in weighing are likely to occur. An assay could be designed to include these errors by using two or more weighings and stock solutions of standard and unknown on each assay. Any statistical formula using the data from one series of, say, 4 plates from the same weighing and dilution can not estimate errors other than those accounting for some measurable

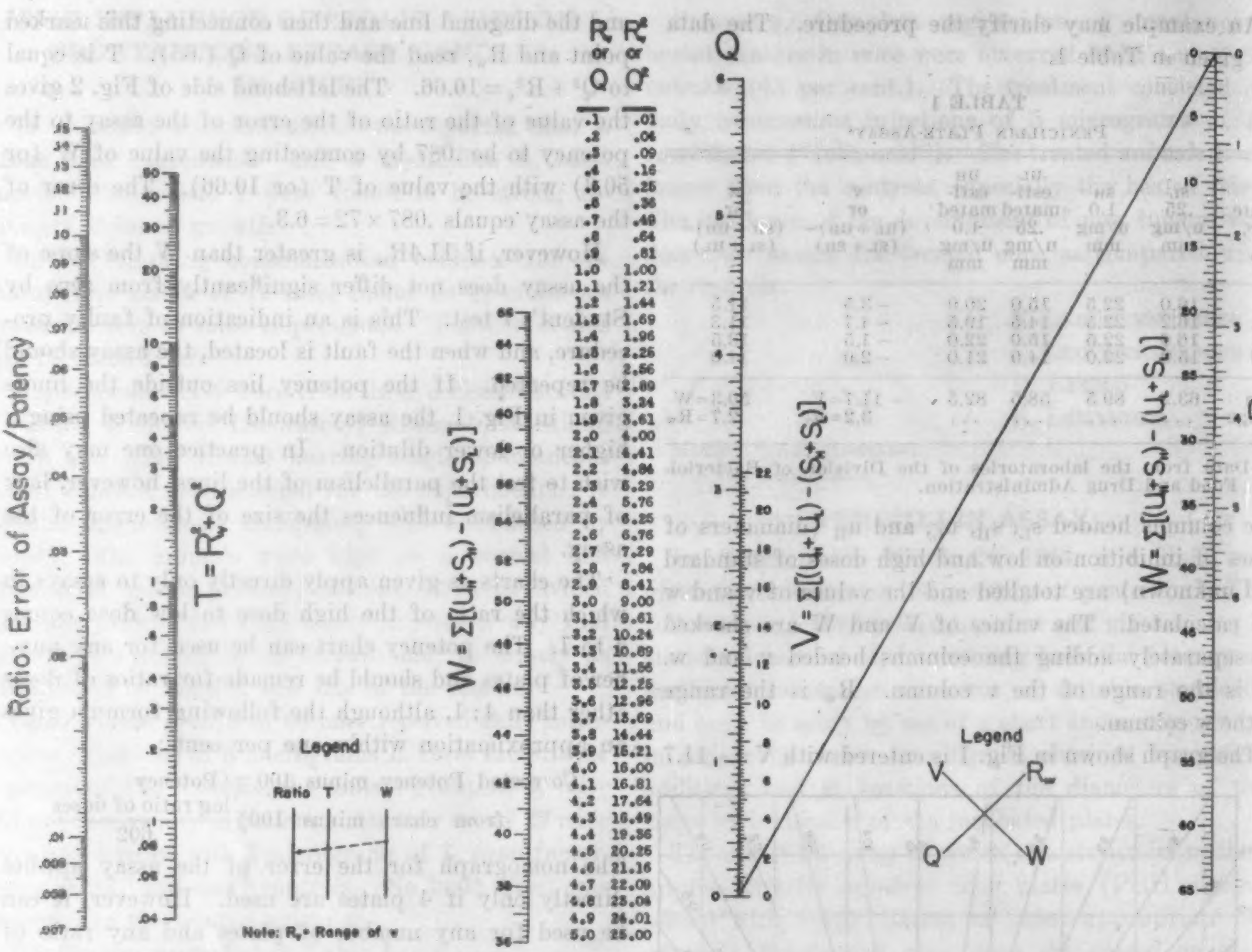

FIG. 2. **Penicillin assay nomographs for estimating the error of the assay from the formula**

$$\frac{\text{Error of Assay}}{\text{Potency}} = \frac{k}{W}\sqrt{R^2_v + \frac{R^2_w V^2}{W^2}}$$

V,W,R_v, and R_w are calculated from the diameters of the zones of inhibition on the two dose, four plate, penicillin assay in which the ratio of doses is 4: 1. A more complete table of squares such as Barlow's "Tables" should be substituted whenever possible for the brief table of squares given between the nomographs. Here k = 1.35, this being ln 4 times the square root of the number of plates all divided by the average number of standard deviations in the range.

variation within the assay. One can not state on the basis of this calculated error of assay that the lot of penicillin was, say, 650 ± 20 units/mg unless the method was so standardized and the results so kept in "statistical control" that any assayists at various laboratories can check each others' results as closely as one assayist can check himself.

The charts and methods can be used in similarly-designed assays of other drugs, *e.g.*, in the Vitamin A assay involving two-dose comparisons of standard and unknown, with four male rats from each litter.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A MANOMETRIC APPARATUS FOR RESPIRATORY STUDIES OF SMALL ANIMALS

THE equipment described below was designed to aid in an investigation of chronic cyanide poisoning in the rat. It is presented because the method has certain advantages not found in other techniques and is adaptable to use in a variety of biological research problems.

The apparatus is essentially a constant volume manometer with a small pump to continuously circulate the gas (Fig. 1). It is simple and inexpensive and except for the air pump may be easily assembled from ordinary laboratory materials. The experimental animal is placed on a screen in a museum jar of about six liters capacity with the groundglass edge sealed with petrolatum to a piece of plate glass. A hole in the top plate contains a rubber stopper through

which pass three glass tubes: a short one just enters the jar, another one reaches about half way down, and the third goes to the bottom of the chamber. Air is circulated through the system by a simple diaphragm pump with glass valves which is operated by a vari-

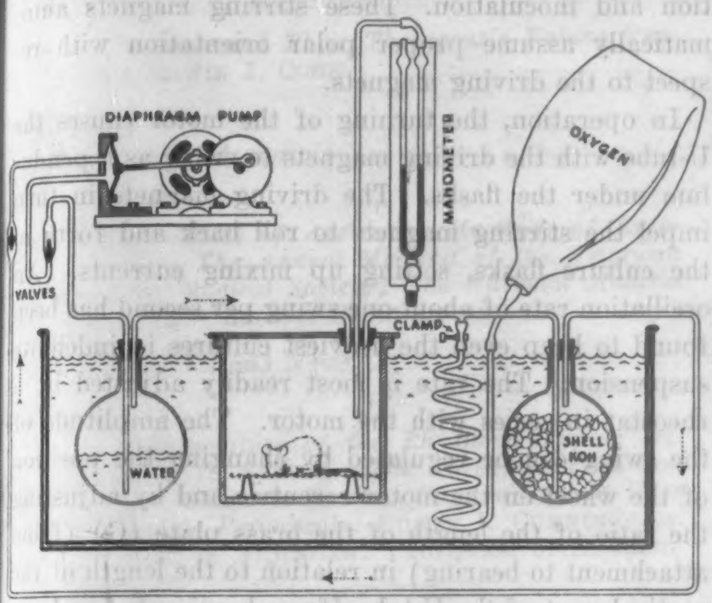

FIG. 1. Diagrammatic sketch of manometric respiration apparatus.

able speed electric motor adjusted to deliver approximately a liter of gas per minute. The air bubbles through a flask of water, enters the top of the animal chamber through the short tube, and is taken out at the bottom by the longest tube. This removal of the bottom layer of gas prevents CO_2 from accumulating in the animal compartment. Carbon dioxide is removed from the air as it passes through the flask containing shell potassium hydroxide, and the dried, CO_2-free gas is then returned to the pump and recirculated. The third tube from the animal compartment leads to a Warburg manometer containing Brodie solution.[1] Changes in the height of this fluid column indicate pressure variations in the system. A T connection to the gas line leads through a coil to a rubber anesthesia bag which contains oxygen for refilling the system. The animal compartment and the flasks are nearly submerged in a constant temperature water bath.

Since the manometer has one end open to the air it is necessary to correct the readings of the fluid column for changes in barometric pressure. This is done with a second manometer, not shown in the sketch, which is connected to a second chamber of approximately the same volume as the total gas space in the first system. This vessel is immersed in the water bath and therefore will compensate for slight temperature changes also.

Before making an oxygen consumption determination, the apparatus is checked for leaks by observing whether it will maintain a positive or negative pressure. The animal is then placed in the chamber in the water bath at 28° C., connections with the air flow line and manometer are made with rubber tubing, and the pump is started. During an initial ten-minute equilibration period the manometer stopcock is closed and the clamp on the line leading to the oxygen bag is left open; since there is a slight positive pressure due to the elasticity of the bag, there is a flow of gas to compensate for any oxygen consumption by the animal. This clamp is closed before manometer readings are started. When the manometer fluid falls to the bottom of the scale more oxygen is admitted by opening the clamp and the fluid is releveled to the 150 mm mark. The system may then be closed and read again within one minute. Since the oxygen is thus quantitatively replaced there is never a significant deficit.

Readings and thermobarometric corrections are made as in the Warburg type of manometer,[1] and a constant for the apparatus may be calculated in the same way if the volume of the system is measured. A simple multiplication of the corrected reading by the constant then gives the volume of oxygen adjusted to normal temperature and pressure.

Since the sensitivity of the system depends upon the gas volume, it is possible to adjust it by altering the size of the animal chamber. The device as illustrated with a volume of about seven liters is sufficiently sensitive to permit readings each minute with an adult rat.

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[1] M. Dixon, "Manometric Methods." Cambridge. 1934.

A MAGNETIC STIRRER FOR CONTINUOUS GAS-FLOW APPARATUS

IN the course of growth studies on the alga *Chlorella*, it was found desirable to compare growth in continuously stirred cultures with that in intermittently stirred cultures. In the latter, 5 per cent. CO_2 in air was bubbled through eight flasks in series. To maintain analogous gas conditions, a simple magnetic stirrer was devised which permitted the same stream of gas to flow through the series of cultures. The accompanying diagram (Fig. 1) shows the essential features of the apparatus.

A constant-temperature bath having a shoulder with a glass inset bottom (A) is employed. In the space below the shoulder is a bank of Mazda lamps (B) that may be adjusted in elevation to vary the intensity of illumination. The lamps are cooled by a fan; and the bath temperature is regulated by a thermostatically controlled heater and refrigerator coil (not shown).

A horizontal rod (C) is fastened to the front of the bath, and from this eight Erlenmeyer culture flasks are supported in the bath over the glass shelf by means of jaw clamps. Each flask is one-third filled with liquid medium containing the algal cells. The gas mixture of 5 per cent. CO_2 in air from a cylinder of compressed gas is bubbled through the vessels connected in series by glass bends and rubber tubing.

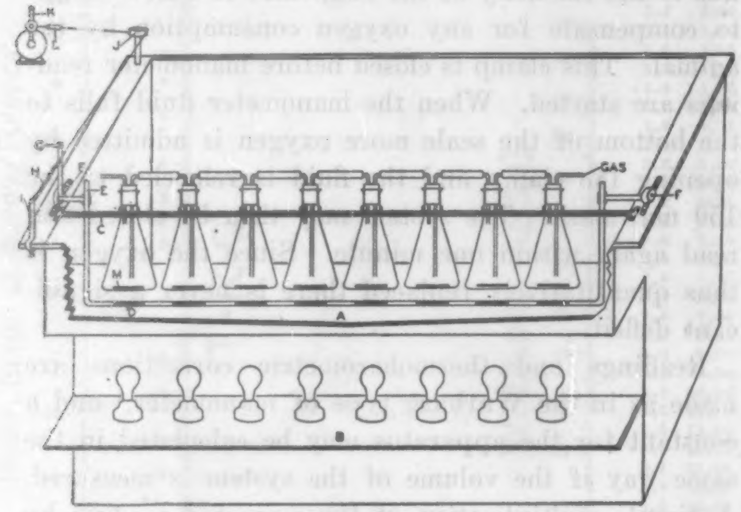

FIG. 1

Stirring of the cultures is effected by paired cylindrical Alnico magnets (4 mm × 45 mm). Eight driving magnets (D) are inserted into a glass tube (4.5 mm bore) with like poles facing, and the tube (E) is bent into a U to fit into the bath. The magnets will tend to distribute themselves equidistantly, but can be moved to desired positions by an externally applied magnet. The U-tube is supported in the bath by clamps attached to wobble bearings (F). Each bearing is made by bending a strap of brass to fit around a roller-skate wheel and then bolting the two together. The lateral extensions of the brass strap are then screwed or clamped to the sides of the bath. These bearings require no lubrication, are practically wear-proof and allow considerable tolerance in alignment of parts. Fastened between the left bearing and its clamp is an upright brass plate (G) (6″ × 1″) with a series of small holes drilled along both edges. A light spring (H) is hooked through a hole in the front edge and connected to a vertical clamp (I) at the corner of the bath. A loop of wire is passed through a hole at the other edge and joined by a braided cord and pulley (J) to an eccentric drive turned by an electric motor. The eccentric is made by attaching a brass bar to the shaft of a reducing gear connected with the motor, drilling a series of holes in the bar, and fastening a roller-skate wheel to it by a wing nut and bolt through one of the holes. The pulley cord is connected to the wheel by a wire loop, and a turnbuckle (L) is inserted to take up slack.

The stirring magnets are similar Alnico cylinders. Each is sealed in Pyrex tubing to render it non-reactive with the cultures. The tubing is thick-walled to withstand mechanical shock, and is thoroughly annealed to eliminate strain. One such stirrer (M) is inserted into each flask of medium prior to sterilization and inoculation. These stirring magnets automatically assume proper polar orientation with respect to the driving magnets.

In operation, the turning of the motor causes the U-tube with the driving magnets to swing as a pendulum under the flasks. The driving magnets in turn impel the stirring magnets to roll back and forth in the culture flasks, setting up mixing currents. An oscillation rate of about one swing per second has been found to keep even the heaviest cultures in indefinite suspension. The rate is most readily adjusted by a rheostat in series with the motor. The amplitude of the swing can be regulated by changing the position of the wheel on the motor eccentric and by adjusting the ratio of the length of the brass plate (G) (from attachment to bearing) in relation to the length of the vertical part of the U-tube (from bearing to bend).

This magnetic stirring arrangement has several advantages over the usual propeller or pump stirrers or shakers. Mechanically, it is simple to construct and operate. Continuous serial gas flow may be maintained through the vessels. Gas connections do not have to be wired to prevent their shaking loose. Single flasks may be removed for sampling without interrupting the agitation of the others. Since stirring is effected within a sealed system, the purity of cultures can be maintained. Actual use has shown that the stirring is gentle but effective and causes no evident damage to the cells. On the contrary, the improvement in the cultural conditions is such that more than double the yield is obtained in half the time. Though originally designed for algal-growth experiments, this magnetic stirrer may well find use in a wide range of biological and chemical procedures in which continuous gentle agitation is desired.

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